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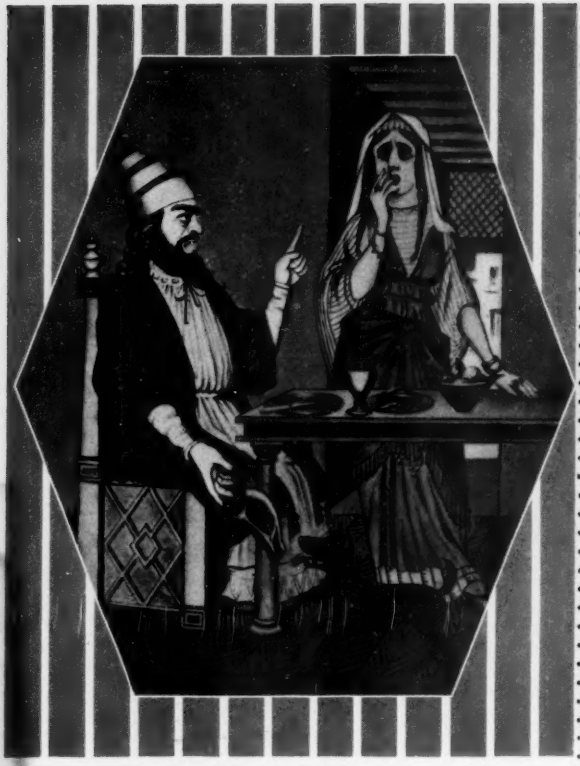

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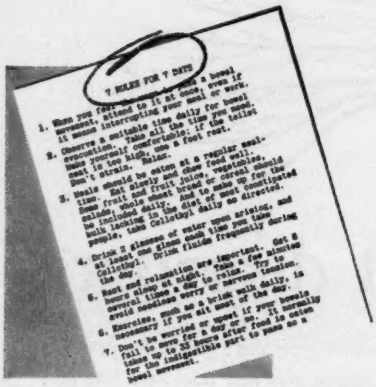

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2. Council on Pharmacy and Chemistry: J. A. M. A. **143**:897, 1950.

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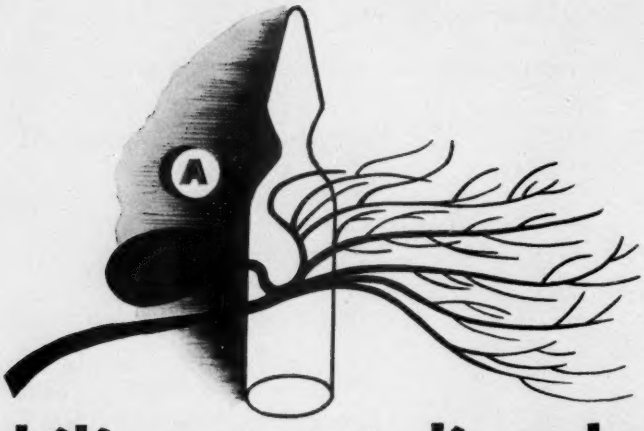

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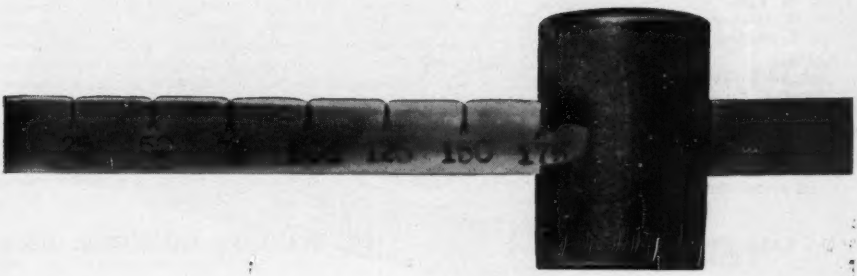

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Report of the Council on Pharmacy and Chemistry, J.A.M.A. 134:527, 1947.

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VOLUME 87 MAY 1951 NUMBER 5

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CORTISONE AND ACTH IN ESSENTIAL HYPERTENSION

Establishment of Renal Glycosuria

HARRIET DUSTAN, M.D.
A. C. CORCORAN, M.D.
ROBERT D. TAYLOR, M.D.
AND
IRVINE H. PAGE, M.D.
CLEVELAND

TREATMENT of normotensive patients with cortisone or pituitary adrenocorticotropic hormone (ACTH) has sometimes resulted in definite increases of arterial pressure.[1] In a hypertensive patient with dermatomyositis, ACTH administration has induced a state resembling hypertensive encephalopathy.[2] A few patients with hypertension have been described as showing some decrease in pressure after treatment with cortisone, so that it has been suggested that cortisone is, paradoxically, sometimes antipressor.[3]

Experimentally, many of the pathological changes elicited by use of desoxycorticosterone in rats are inhibited or reversed by treatment with adrenal cortex extracts or with ACTH.[4] These lesions include an arterial disease which is similar to that observed in human beings suffering from severe hypertension.[5] Thus, quite

---

Dr. Dustan is a United States Public Health Service Postdoctorate Research Fellow.

From the Research Division and the Frank E. Bunts Educational Institute, Cleveland Clinic Foundation.

1 (*a*) Sprague, R. C.; Power, M. H.; Mason, H. L.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199 (Feb.) 1950. (*b*) Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

2. Elkinton, J. R.; Hunter, A. D., Jr.; Godfrey, L.; McCory, W. W.; Rogerson, A. C., and Stokes, J.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **141**:1273 (Dec. 31) 1949.

3. (*a*) Perera, G. A.; Pines, K. L.; Hamilton, H. B., and Vislocky, K.: A Clinical and Metabolic Study of 11-Dehydro-17-Hydroxy-Corticosterone Acetate (Kendall Compound E) in Hypertension, Addison's Disease and Diabetes Mellitus, Am. J. Med. **7**:56, 1949. (*b*) Perera, G. A.; Fleming, T. C.; Pines, K. L., and Crymble, M.: Cortisone in Hypertensive Vascular Disease, J. Clin. Investigation **29**:139, 1950.

4. Woodbury, D. M.; Rosenberg, C. A., and Sayers, G.: Antagonism of Adrenocorticotropic Hormone (ACTH) and Adrenal Cortical Extract (ACE) to Desoxycorticosterone (DCA): Pathological Changes, Federation Proc. **9**:139, 1950.

5. Masson, G. M. C.; Hazard, J. B.; Corcoran, A. C., and Page, I. H.: Experimental Vascular Disease Due to Desoxycorticosterone and Anterior Pituitary Factors: II. Comparison of Pathological Changes, Arch. Path. **49**:641 (June) 1950.

apart from the possible antipressor effects of cortisone or ACTH, there is a basis for supposing that they might favorably influence hypertensive vascular disease as such.

Our purpose here is to record effects of such treatment on arterial pressure in four patients with severe essential hypertensive vascular disease. We shall also describe observations on other vascular, renal and, in outline, metabolic functions. The renal tubular reabsorption of glucose was measured by specific means.

METHODS

Of four patients with severe essential hypertensive vascular disease, two were given cortisone and two ACTH. They were selected after long periods of observation in the hospital on these or previous admissions. Blood pressure levels and functional status were known to be stable. The vascular disease, while severe, was not rapidly progressive.

Patients 1 and 2 received 25 mg. of cortisone acetate intramuscularly every six hours for 12 days. Treatment was repeated in patient 1 in two subsequent periods. During the second period he received 25 mg. of cortisone every six hours for nine days, then 50 mg. every 12 hours for 25 days. In the third period he received 25 mg. of cortisone every six hours for three days and 50 mg. every 12 hours on the three subsequent days. Patients 3 and 4 received 25 mg. of ACTH intramuscularly every six hours for 12 days.

Blood pressure measurements were made at rest each morning and late afternoon and were summarized statistically.[6] The patients were weighed daily before breakfast.

The dietary intakes were kept as constant as possible. During all three periods of study, patient 1 received a low sodium diet based on lonolac,® a sodium-free powdered milk preparation, with daily intakes of 2,000 to 2,800 calories, 13 Gm. of nitrogen and 6 to 8 milliequivalents of sodium. To this in the first period were added 6 Gm. of sodium chloride (110 milliequivalents of sodium) and 180 Gm. of resodec®,[7] an ammonium-potassium cationic exchange resin. In the second period use of Amberlite was discontinued, and in the third period no extra salt was given. Patient 2 received a lonolac® low sodium diet, with daily intakes of 2,000 to 2,200 calories, 6 to 8 milliequivalents of sodium and 10 Gm. of nitrogen. During the control period patient 3 received a diet containing 1,200 calories, 35 milliequivalents of sodium and 6.6 Gm. of nitrogen, and patient 4 was given 1,500 calories with 16 milliequivalents of sodium and 9.2 Gm. of nitrogen. During ACTH treatment dietary intakes had to be increased because of increased appetite.

Urinalyses were made on 48 or 72 hour pooled specimens and, in patient 1 in the third period of study, on 24 hour specimens. Urinary "hypobromite-N," sodium, creatinine and corticoids were determined by methods noted elsewhere[8] and sugar by clinitest® reagent tablets. Blood sugar, urea, plasma carbon dioxide–combining power and serum chloride, potassium and total base were determined by standard clinical methods. Dr. Arnold Lazarow made the analyses of blood glutathione. Methods used in measurements of renal hemodynamics, tubular secretory capacity for paraaminohippurate (T_{mPAH}), glucose reabsorptive capacity (T_{mG}), concentrating power, urinary protein and sediment are described elsewhere.[9] Plasma and extracellular fluid volumes were measured as the volumes of distribution of Evans blue dye and thiocyanate, respectively.

---

6. Hill, A. B.: Principles of Medical Statistics, ed. 3, London, The Lancet, Ltd., 1945.

7. This preparation was furnished by Mr. W. Swain, of Smith, Kline & French Laboratories, Philadelphia 1.

8. (*a*) Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Controlled Observations on the Effect of Low Sodium Dietotherapy in Essential Hypertension, Circulation **3**:1 (Jan.) 1951. (*b*) Corcoran, A. C., and Page, I. H.: Methods for the Chemical Determination of Corticosteroids in Urine and Plasma, J. Lab. & Clin. Med. **33**:1326, 1948.

9. Page, I. H., and Corcoran, A. C.: Arterial Hypertension: Its Diagnosis and Treatment, ed. 2, Chicago, The Year Book Publishers, Inc., 1949. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, ed. 1, New York, The Commonwealth Fund, 1944.

Relative vascular responsiveness was measured from the intra-arterial pressure responses to standard doses of epinephrine, arterenol and tetraethylammonium chloride and to the cold pressor test by a method which will be reported elsewhere.[10] Sweat sodium estimations were done by an adaptation of Conn's [11] procedure.

Other observations included examination of the fundi, teleroentgenographic measurements of heart size and electrocardiograms.

Pretreatment control observations extended over nine to 11 day periods and post-treatment observations over 16 days.

RESULTS

Blood Pressures.—Data are summarized in table 1. Patient 1 showed a significant reduction in systolic arterial pressure during the first period of treatment with cortisone, but in the two subsequent periods this was not observed. Of the

TABLE 1.—*Statistical Summary of Observations on Arterial Pressure*

Patient				Blood Pressure, Mm. Hg				Number of Observations
No.	Course	Period *	Days	Mean Systolic	Mean Diastolic	Systolic	Diastolic	
1	1	1	1 to 11	164	106	15.6	10.4	24
		2	12 to 23	137	96	17.7	11.6	24
		3	24 to 26	153	103	....	....	7
		4	33 to 41	154	101	17.1	10.7	18
	2	1	1 to 14	190	117	9	7.7	27
		2	15 to 49	195	118	17	9.6	66
		3	50 to 63	185	120	14.6	8.1	28
	3	1	1 to 14	187	121	13.4	7.0	27
		2	15 to 20	186	121	9.3	4.5	12
		3	21 to 35	184	119	15.0	8.5	28
2	1	1	1 to 11	194	132	18.7	13.6	21
		2	12 to 23	195	132	16.8	20.1	23
		3	34 to 41	176	117	12.3	11.8	17
3	1	1	1 to 9	223	151	23.7	15.9	18
		2	10 to 21	201	136	22.1	20.0	23
		3	31 to 38	209	139	16.6	11.7	15
4	1	1	1 to 9	231	141	18.9	13.1	18
		2	10 to 21	238	138	22.0	14.3	24
		3	22 to 24	192	117	....	....	8
		4	30 to 37	222	140	16.4	12.2	14

* Period 1 is control foreperiod; period 2 is treatment period. Periods 3 and 4 are post-treatment control periods. Indexes of significance (difference between mean pressures divided by the standard error of the difference) are as follows: Patient 1, course 1, periods 1 and 2, systolic 5.6, diastolic 2.3; periods 1 and 4, 2.0 and 1.4, respectively. In course 2 these values for periods 1 and 2 and 1 and 3 are less than 1.5. In course 3, for similar periods, they are less than 1.0. Patient 2, periods 1 and 2, values are less than 1.0; periods 1 and 3, systolic 4.0 and diastolic 3.0. Patient 3, periods 1 and 3, systolic 2.0, diastolic 0.6. Patient 4, periods 1 and 2 and 1 and 3, values are less than 2.0.

two patients treated with ACTH, one patient (3) showed a slight decrease in systolic arterial pressure during treatment. This is statistically, although not clinically, significant. The other patient (4) exhibited no definite change.

In the first post-treatment period blood pressure persisted at slightly less than control levels in patient 1, although the differences are not statistically significant. No decrease was seen following treatment in the two subsequent periods. Patient 2 displayed significant decreases in both diastolic and systolic blood pressure after treatment was stopped. In the patients treated with ACTH, the arterial pressures

10. Spankus W., and Page, I. H.: Unpublished observations.

11. Conn, J. W.: Electrolyte Composition of Sweat: Clinical Implications as an Index of Adrenal Cortical Function, Arch. Int. Med. **83**:416 (April) 1949.

after treatment were also somewhat lower than in the control period. The differences are neither impressive nor statistically significant. Scanty data immediately after interruption of treatment in patient 4 suggest that there may have been a definite but transient decrease in pressure.

No definite changes occurred in pressor responsiveness to epinephrine, arterenol, tetraethylammonium chloride, the Valsalva maneuver or the cold pressor test in the patients treated with cortisone. The patients treated with ACTH may have manifested slight increases in pressor responses to epinephrine, arterenol and the cold pressor test, but the significance of the slight changes observed cannot yet be assessed.

Renal Functions.—A. Concentrating Power, Proteinuria and Sediment Count: There was no change in concentrating power, proteinuria and sediment count either during or after treatment.

TABLE 2.—*Observations of Specific Renal Functions*

Patient			Cc. per Min.			Mg. per Min.		
No.	Course	Day	R. B. F.*	G. F. R.†	F. F.‡	Tm_{PAH} §	Tm_G ‖	P_m ¶
1	1	Control	719	80	0.19	75	207	148
		23	804	87	0.18	76	275	119
		48	...	..	....	..	173	...
	2	Control	743	91	0.21	61	275	149
		44	804	110	0.25	63	240	157
		80	702	94	0.23	63	...	154
2	1	Control	305	52	0.28	27	64	158
		22	244	40	0.27	28	29	171
		44	...	..	....	..	33	...
3	1	Control	542	90	0.28	65	200	193
		21	788	96	0.22	74	110	142
		43	...	..	....	..	90	...
4	1	Control	459	68	0.25	40	121	185
		22	440	67	0.29	48	90	184
		42	...	..	....	..	70	...

* R. B. F. means renal blood flow from the plasma clearance of paraaminohippurate and the venous hematocrit.

† G. F. R. means rate of glomerular filtration.

‡ F. F. means filtration fraction.

§ Tm_{PAH} indicates tubular secretory capacity for paraaminohippurate.

‖ Tm_G means tubular reabsorptive capacity for glucose. These values are corrected to 1.73 square meters of body surface.

¶ P_m indicates average arterial pressure during the test as mean of systolic and diastolic auscultatory pressures.

B. Renal Blood Flow, Filtration Fraction, Tm_{PAH} and Tm_G: The data are presented in table 2. Patient 1 showed an increase in renal blood flow during the first course of cortisone therapy. However, this function was slightly depressed in patient 2, slightly increased in patient 3 and unchanged in patient 4. Renal resistance usually varied inversely to blood flow. No definite changes in filtration rate were observed.

Of greater interest were the changes in tubular reabsorptive capacity for glucose (Tm_G). In patient 1 this function was somewhat increased during both the first and the second course of treatment with cortisone. In patient 2 treated with cortisone and patients 3 and 4 treated with ACTH, it was depressed during treatment and persisted at low levels during the post-treatment observations.

Metabolic Changes.—A. Nitrogen Equilibrium: This function was derived from estimates of daily food intakes and of urinary "hypobromite-N." The approximation of nitrogen balance thus found was validated in some degree by concurrent measurements of urinary nitrogen-creatinine ratio, an increase in which is taken as evidence of protein catabolism. The two patients treated with cortisone showed in the first three days decreases in urinary nitrogen consistent with protein storage, and in patient 2 there was a depression of the urinary nitrogen-creatinine ratio. Later, patient 1 showed an increased urinary nitrogen excretion, while in patient 2 the urinary nitrogen excretion did not increase until the post-treatment period. Of the patients treated with ACTH one (3) did not seem to go into negative nitrogen balance. Increased urinary nitrogen was accounted for by a proportional increase in nitrogen intake. The other patient (4) also had increased nitrogen intake during

TABLE 3.—*Measures of Adrenal Cortex Function* *

Patient 1								
Course 1			Course 2			Course 3		
Days	Urinary Corticoids, Mg./Day	Sweat Sodium, mEq./L.	Days	Urinary Corticoids, Mg./Day	Sweat Sodium, mEq./L.	Days	Urinary Corticoids, Mg./Day	Sweat Sodium, mEq./L.
1 to 11	1.8	15	1 to 14	1.08	28.6	7 to 14	1.52	..
12 to 14	1.6	..	15 to 23	0.8	....	15 to 17	1.39	..
15 to 17	1.9	..	24 to 32	2.2	29.2	18 to 20	1.31	..
18 to 20	1.3	..	33 to 42	3.4	....	21 to 28	1.51	..
21 to 23	3.1	21	43 to 49	4.4	....	.....	....	..
24 to 26	2.2	..	50 to 59	1.7	13.3 †	.....	....	..
38 to 41	1.36	20	60 to 62	0.6	....	.....	....	..
Patient 2			Patient 3			Patient 4		
1 to 11	1.09	20	1 to 9	0.84	81	1 to 9	1.5	8
12 to 14	1.4	..	10 to 12	...	..	10 to 12	2.8	..
15 to 17	0.96	19	13 to 15	1.7	..	13 to 15	5.0	..
18 to 20	0.93	..	16 to 18	1.4	16	16 to 18	11.7	19
21 to 23	1.4	..	19 to 21	2.6	..	19 to 21	11.1	..
24 to 25	0.9	..	22 to 30	0.73	..	22 to 24	2.6	..
26 to 28	1.5	..	31 to 38	0.55	48	30 to 32	0.74	..
29 to 41	1.4	24	.....	...	..	33 to 37	0.72	18

* Urinary formaldehydogenic corticoids in milligrams per 24 hours averaged during successive periods of study. Observations on concurrent sweat sodium concentrations are recorded at intervals during the periods of urine collection.

† Average of five determinations.

treatment, but nitrogen excretion was disproportionately increased and the nitrogen-creatinine ratio elevated, indicating a negative balance. During three days immediately after treatment there was evidence of positive nitrogen balance.

B. Sodium Excretion: The two patients treated with cortisone and one of the patients (3) treated with ACTH showed notable decreases in urinary sodium during treatment. In patient 4, sodium excretion was increased during part of the period and at no time was there significant sodium retention. During the post-treatment period patients 2 and 4 exhibited increases in urinary sodium above control levels while the others did not.

Interpretation of urinary sodium determinations in patient 1 (first period) is complicated by the administration of resodec® resin. The equivalent of a low sodium intake was achieved by concurrent treatment with the resin and sodium chloride. The low urinary sodium value substantiates this assumption. His sodium intake

and output were high during the second course of treatment and the intake low during the third.

C. Body Weight and Fluids: Body weights were not notably altered by treatment or by its discontinuance. Blood and plasma volumes and the volumes of distribution of thiocyanate varied irregularly, tending somewhat to decrease during treatment. The changes are neither large nor consistent and need not be reported in detail.

Adrenal Cortex Function.—A. Urinary Corticoids (table 3): With cortisone treatment patients 1 (first course) and 2 showed no consistent changes in urinary corticoids. With ACTH administration patient 3 showed a slight increase and patient 4 a marked increase. During the immediate post-treatment period, values for patients 1, 2 and 3 persisted in the range of control levels. In patient 4 the values obtained in the two days immediately after treatment remained higher than

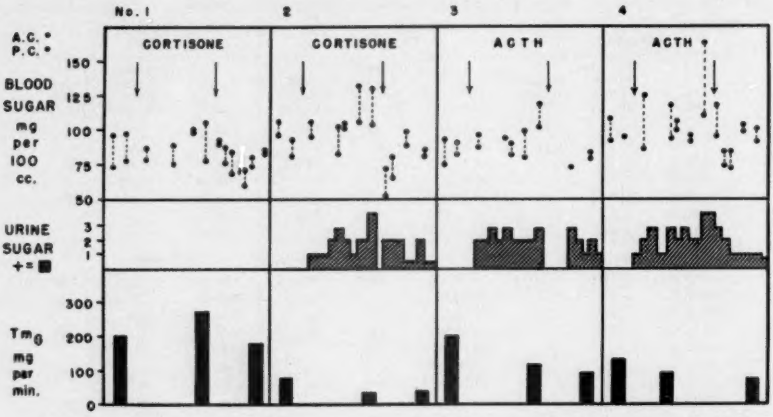

Chart showing blood sugar levels before (*A.C.*) and 2½ hours after (*P.C.*) meals. Vertical arrows indicate beginning and end of treatment periods. The urinary reaction for sugar is indicated conventionally as 1 to 4+ and was determined on four fractionated daily specimens. 1+ indicates the appearance of a reaction for glucose in one specimen and 4+ its appearance in all specimens. Tm_G indicates maximal tubular reabsorptive capacity for glucose expressed as milligrams per minute per 1.73 square meters of body surface.

the controls but later fell to subcontrol levels. In the second course of treatment patient 1 showed a stepwise increase in corticoid output, followed by a decrease after cortisone administration was discontinued. The excretion values were not significantly changed in the third course.

B. Sweat Sodium Concentrations: These are listed in table 3. Patients 1 (first course) and 2 showed low normal values in control periods, which were not altered by treatment with cortisone or by discontinuing it. As noted above, patient 1 was effectively on a low sodium ration at this time. Patient 1 had a decrease of sweat sodium in the post-treatment period while still on a high sodium diet. Patient 2 was on a low sodium ration without supplements. Patient 4 on a much less restricted sodium intake also showed low control values which were not altered by ACTH

treatment. Patient 3 on a low sodium ration showed a normal sweat electrolyte concentration which was depressed by administration of ACTH.

C. Blood and Urine Sugar, Cholesterol and Electrolytes: In all four patients the fasting blood sugar levels (fig.) rose moderately during the treatment period but never reached abnormally high levels. The blood glucose levels 2½ hours after meals (p.c.) also rose, and in patients 2 and 4 they became abnormally elevated during the last two days of treatment. Mild glycosuria appeared in the patients treated with ACTH before any other indication of impaired dextrose tolerance. One of the patients treated with cortisone showed a similar persistent glycosuria. There were no consistent changes in fasting blood glutathione levels in either group.

In all four patients total serum cholesterol diminished during and rose after treatment. The more striking changes occurred in those treated with ACTH. For patients 1, 2, 3 and 4 the falls during treatment were 19.2, 26.8, 39.2 and 34.2 per cent, respectively, while the post-treatment elevations above control levels were 23, 32.2, 55.2 and 64.5 per cent, respectively.

There were no notable changes in serum electrolytes other than moderate decreases of serum potassium during treatment in the patients receiving ACTH.

D. Other Functions: There were no significant changes in the electrocardiogram and heart size. Patient 1 was euphoric during all three courses of treatment with cortisone. There was little mood change in patient 2. Patients 3 and 4 both experienced an increased sense of well-being.

COMMENT

One patient (1) demonstrated a statistically significant fall in systolic blood pressure during the first cortisone treatment period. This was associated with a decrease in urinary sodium and evidence of renal vasodilatation. This patient had been shown to respond to sodium restriction by a decrease of arterial pressure in a previous study.[8a] Since the depressor effect observed during the first treatment period was not reproduced during the second (high sodium) and third (low sodium) periods, it can hardly be ascribed to cortisone treatment as such. The decrease of urinary sodium in the first period is consistent with either sodium retention or increased extrarenal sodium loss. The fact that the blood pressure fell suggests that sodium was, in fact, somehow being lost from the body.

The second patient who received cortisone (2) showed a statistically significant fall in both diastolic and systolic blood pressure levels during the post-treatment period. This might be attributed to "compensatory" depression of adrenal cortex function.

If one accepts this explanation of the fall in pressure after cortisone administration, then it follows that it must have been cortisone and not full normal adrenal activity which helped maintain pressure at hypertensive levels during the later days of treatment. On this assumption, a variable balance between the adrenal-inhibiting and pressure-sustaining effects of cortisone may explain the changes of blood pressure observed elsewhere in hypertensive patients.[8]

With ACTH as with cortisone, the responses were in some degree disparate. One patient showed a slight decrease of pressure and renal vasodilatation during treatment and slight rise in pressure thereafter. The pressure of the other patient,

as well as the renal status, was unchanged by treatment. It may have been that pressure was transiently decreased after treatment.

Metabolic Changes.—The observations made and reported in outline are consistent with those demonstrated in more precise metabolic studies [1a] during treatment with these hormones. Cortisone in the dose given had small but disparate effects on nitrogen equilibrium in the two patients, and only one of these showed some hyperglycemia. One of the two ACTH-treated patients went into what seemed to be a definitely negative nitrogen balance which was associated with hyperglycemia. The seeming irresponsiveness of the other ACTH-treated patient, reflected in the values of urinary corticoids, may perhaps be a sequel to a year long treatment with bacterial pyrogens which had been terminated six months before. Three of the four patients showed sodium retention. Interestingly, patient 4 during treatment with ACTH failed to retain sodium and would seem also to have lost potassium, since serum potassium decreased from 4.9 to 3.2 milliequivalents per liter.

The effects of ACTH treatment on serum cholesterol parallel those of Conn,[12] although he did not emphasize the "rebound" to high levels after treatment stopped. The less severe, but no less regular, depression of cholesterol during treatment with cortisone and its "rebound" contrast with his observations and those of others on the effects of the hormone in patients with Addison's disease and in normal subjects.[12] Since these persons were hypertensive, it is interesting that a decrease of ester cholesterol has been found in one hypertensive person treated with cortisone.[3b]

Urinary Corticoids.—Cortisone administration had no effect on the excretion of chloroform-extractable, "free" formaldehydogenic steroids in patient 1 (first period) and patient 2. However, while like dosage had no effect in patient 1 during his second course, a shift in dosage schedule from four times to twice daily caused a progressive increase in output. This may reflect an overloading of the mechanisms of hormone utilization and conjugation. This change in output was not demonstrated during his third brief course of treatment. Use of ACTH caused the expected rise in steroid output in patient 4. The small effect seen in patient 3 is commented on above.

Glycosuria.—Treatment with ACTH has been observed to cause glycosuria before it causes hyperglycemia or other evidence of impaired glucose metabolism.[13] It has been supposed, though not proved, that this glycosuria was in part renal. The decreases of glucose Tm found in three of four patients in this study and the correspondence of these changes with glycosuria (fig.) indicate that the glycosuria is renal and due to depression of tubular glucose reabsorption. It can be assumed that glucose reabsorption involves phosphorylation; it may be that induced hypercorticoidism impairs the renal tubular hexokinase function in much the same fashion

12. Conn, J. W.; Vogel, W. C.; Louis, L. H., and Fajans, S. S.: Serum Cholesterol: A Probable Precursor of Adrenal Cortical Hormones, in Pituitary-Adrenal Function, edited by R. C. Christman, New York, Science Press Printing Company, 1951. Adrenal Cortex, Transactions of the First Conference, March 7-8, 1949, edited by E. P. Ralli, New York, Josiah Macy, Jr., Foundation, 1950.

13. Browne, J. S. L.: Effect of Corticotropin on Nitrogen and Carbohydrate Metabolism, in Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, New York, Josiah Macy, Jr., Foundation, 1943. Conn, J. W.; Louis, L. H., and Wheeler, C. E.: Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone: Relation to Uric Acid Metabolism, J. Lab. & Clin. Med. **33**:651, 1948.

that adrenal hormones inhibit the hexokinase reaction in vitro.[14] This renal tubular dysfunction cannot be correlated with changes in blood glutathione. Our data indicate that in some patients decreased glucose reabsorptive capacity is an early and persistent result of hypercorticoidism.

SUMMARY

Cortisone or pituitary adrenocorticotropic hormone (ACTH) in doses of 100 mg. daily had no definite or reproducible effects on arterial pressure in each of two pairs of patients with severe essential hypertensive vascular disease, although pressure decreased briefly in two after treatment was stopped.

Of the specific renal functions (renal blood flow, glomerular filtration and tubular secretory capacity for paraaminohippurate [Tm_{PAH}]) renal blood flow was increased in two patients (one receiving cortisone and one receiving ACTH).

Urinary corticoids were not consistently increased in two patients given cortisone but were increased in those receiving ACTH. ACTH treatment also depressed sweat sodium concentration in one patient, but, like cortisone, it had no effect on patients with low control levels of sweat sodium due to dietary restrictions.

All four patients showed decreased serum cholesterol concentrations during treatment and a "rebound" to greater than control levels in the post-treatment period.

Three of the four patients showed a decrease of maximum renal tubular reabsorptive capacity for glucose (Tm_G) during treatment. This persisted into the post-treatment period and was associated with glycosuria. Depression of this renal function seems to be an early and lasting result of hypercorticoidism.

14. Colowick, S. P.; Cori, G. T., and Slein, M. W.: The Effect of Adrenal Cortex and Anterior Pituitary Extracts and Insulin on the Hexokinase Reaction, J. Biol. Chem. **168**:583, 1947.

EXPERIENCES IN THE USE OF A LOW SODIUM DIET IN THE MANAGEMENT OF ASCITES

ROSWELL W. PHILLIPS, M.D.
AND
ARTHUR M. PHILLIPS, M.D.
PROVIDENCE, R. I.

SINCE sodium excretion is greatly reduced in cirrhotic patients forming ascitic fluid [1] and the formation of ascitic fluid has been shown to be directly proportional to sodium intake,[2] a logical plan of therapeutic management might include consideration of this factor.

We have studied the influence of restricted sodium intake on the clinical course of ascites in patients with Laennec's cirrhosis. All the patients presented a clearcut picture of the disease, with ascites as a prominent feature.

During a control period the patients received a high protein, high carbohydrate, low fat diet without salt restriction. In addition, during their period of hospitalization they received supplementary vitamins, methionine and liver extract intramuscularly. After the control period a special diet was instituted, consisting of 3,400 calories and containing 135 Gm. of protein and 605 mg. of sodium. Records were kept of the daily weight fluid intake and output and urinary chloride excretion. Liver function tests were carried out at various intervals. The urinary chloride determinations were made with the use of a modification of the method described by Fantus.[3]

REPORT OF CASES

CASE 1.—M. M., a 54 year old Italian male bartender, had been a heavy whisky drinker for four years and had eaten only one meal daily during most of that time. Six months prior to admission swelling of his abdomen and legs had developed. Since that time, he had required abdominal paracenteses at intervals of two to three weeks. These were carried out at another hospital.

From the Medical Service, Veterans Administration Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Goodyer, A. B.; Relman, A. S.; Lawrason, F. D., and Epstein, F. H.: Salt Retention in Cirrhosis of the Liver, J. Clin. Investigation **29**:973 (Aug.) 1950.

2. (*a*) Faloon, W. W.; Eckhardt, R. D.; Cooper, A. M., and Davidson, C. S.: The Effect of Human Serum Albumin, Mercurial Diuretics and a Low Sodium Diet on Sodium Excretion in Patients with Cirrhosis of the Liver, J. Clin. Investigation **28**:595 (July) 1949. (*b*) Eisenmenger, W. J.; Ahrens, E. H., Jr.; Blowdheim, S. H., and Kunkel, H. G.: The Effect of Rigid Sodium Restriction in Patients with Cirrhosis of the Liver and Ascites, J. Lab. & Clin. Med. **34**:1029. (Aug.) 1949.

3. Fantus, B.: Fluid Postoperatively: Statistical Study, J. A. M. A. **107**:14 (July 4) 1936.

The past history disclosed treatment for syphilis at the age of 24. The family history was noncontributory. Physical examination revealed an emaciated white man appearing chronically ill. His chest was increased in the anteroposterior diameter. Spider angiomas and dilated veins were present in the skin of the chest and abdominal wall. A moderate amount of ascitic fluid was present, and the liver was palpable 4 fingerbreadths and the spleen 2 fingerbreadths below the costal margin. A reducible umbilical hernia was noted.

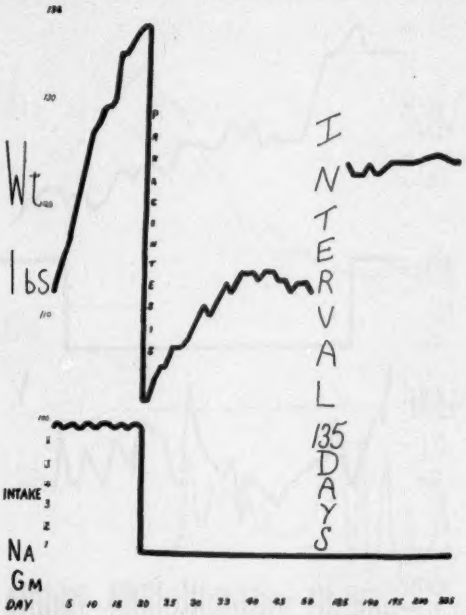

Fig. 1.—Chart showing course in the hospital in case 1 (patient M. M.).

TABLE 1.—*Results of Liver Function Studies in Case 1 (M. M.)*

Hospital Day	1	7	60	88	138	174
Albumin, Gm./100 cc.	2.8	2.5	4.4	3.6	2.6	3.9
Globulin, Gm./100 cc.	3.0	3.1	1.5	1.9	1.9	1.9
Thymol, units	...	...	4	...	3	1
Bilirubin, mg./100 cc.	...	...	...	...	...	0.4
Sulfobromophthalein retention, % *	5	5	...	...	...	...

* Retention of 5 mg. dose 45 minutes after administration.

Course in the Hospital.—During the control period rapid accumulation of ascitic fluid took place, with a gain of weight (fig. 1) from 112 to 136 pounds (50.8 to 61.7 Kg.). Paracentesis was done, and 10 quarts (9.5 liters) of fluid was withdrawn, causing a drop in weight to 102 pounds (46.3 Kg.). The special low sodium, high protein diet was then begun. Reaccumulation of some ascitic fluid occurred, but at a slow rate with the body weight leveling off at 114 pounds (51.7 Kg.). The increase in weight during the remainder of his hospital stay was due to gain in tissue and not in ascitic fluid. By the time of discharge a minimal amount of fluid was present, with no evidence that reaccumulation was taking place. He was seen six months later, at which time he was asymptomatic and had no ascites; the liver and spleen were palpable as on admission, and he was working at his occupation as bartender.

Case 2.—J. M., a 50 year old white man, with alcoholism of 18 years' duration, was found to have evidence of Laennec's cirrhosis one year before admission, while at another hospital. He was, however, relatively asymptomatic until two months before admission, when he noted progressive abdominal swelling, anorexia and vomiting, dark urine and watery diarrhea.

The past history and family history were noncontributory. Physical examination disclosed a well developed and well nourished white man with icterus of the scleras and evidence of moderate ascites. The liver and spleen were not felt.

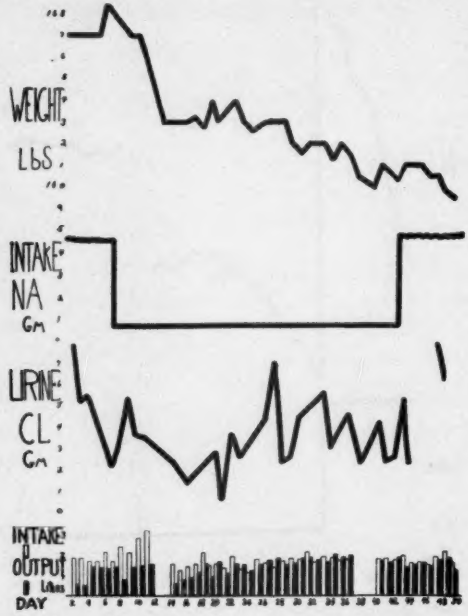

Fig. 2.—Chart showing course in the hospital in case 2 (patient J. M.).

Table 2.—*Results of Liver Function Studies in Case 2 (J. M.)*

Hospital Day	1	16	30
Albumin, Gm./100 cc.	4.7	4.5	4.8
Globulin, Gm./100 cc.	3.2	2.6	2.5
Thymol, units	2	2.5	2
Bilirubin, mg./100 cc.	1.3	1.07	0.7
Prothrombin time, % of normal	68	59	59

Course in the Hospital.—During the control period the patient ate well. His accumulation of fluid remained stationary and then increased slightly in amount. After institution of the special diet, the ascites diminished rapidly, and by his thirty-sixth hospital day it was no longer evident (fig. 2). Resumption of the control period diet on his forty-second hospital day was not followed by reaccumulation of fluid. As noted in table 2, the results of liver function tests became normal by discharge.

Case 3.—E. F., a 36 year old white man, had been a chronic alcoholic for five years, during which time his food intake had been poor. He had vomited frequently and had noted small

hematemeses on 15 occasions. For two weeks before admission he had experienced progressive swelling of his abdomen and legs.

The past history and family history were noncontributory. Physical examination revealed a well developed white man with wasting of muscles and subcutaneous tissue. There were spider angiomas of the skin of the neck and numerous dilated veins both anteriorly and posteriorly over the chest and abdomen. A venous hum was audible at the umbilicus. The abdomen was rounded with obvious ascites, and edema of legs and feet (3+) was present. There were tremor of the tongue and extremities, absence of ankle jerks and hyperesthesia of the soles.

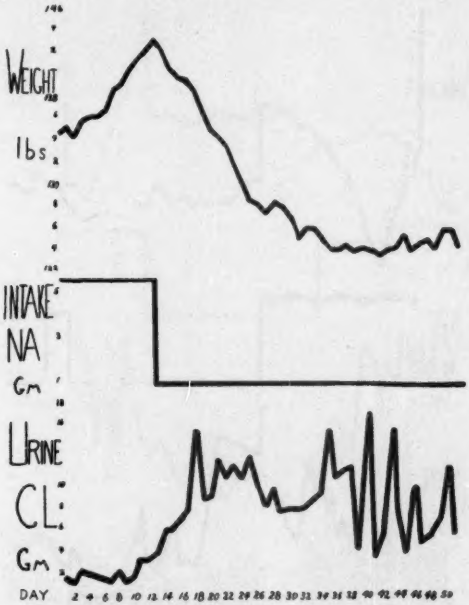

Fig. 3.—Chart showing course in the hospital in case 3 (patient E. F.).

TABLE 3.—*Results of Liver Function Tests in Case 3 (E. F.)*

Hospital Day	1	6	28	50
Albumin, Gm./100 cc.	1.3	3.5	4.1	4.5
Globulin, Gm./100 cc.	3.5	2.5	3.4	3.6
Thymol, units	4	6	4	6
Bilirubin, mg./100 cc.	1.1	0.9	0.79	1.0
Prothrombin time, % of normal	59	81	81	68

Course in the Hospital.—The patient had a low grade fever during the first 30 hospital days. This was thought to be associated with activity of the liver disease. During the control period he ate well, but a gradual increase in his weight (due to ascites) occurred (fig. 3). Results of his liver function tests are noted in table 3. After institution of the low sodium, high protein diet, a striking loss of the ascites and edema took place. The visible evidence of portal collateral circulation present on admission largely disappeared, so that by discharge on his sixty-third hospital day only a few dilated veins on the anterior abdominal wall were present. By his thirty-fourth hospital day all evidence of ascites and edema had disappeared, and no further accumulation took place. The liver was palpable 3 fingerbreadths and the spleen 2 fingerbreadths below the costal margin.

CASE 4.—A. A., a 55 year old white male cook, entered the hospital with a two months' history of progressive swelling of his abdomen and ankles. He had been a heavy drinker of beer and whisky and had eaten poorly. He had been treated for syphilis 25 years before entry, and the reaction to a serologic test performed two years ago was said to be negative.

Physical examination revealed the abdomen to be tense with ascitic fluid; dilated superficial veins were present, as were spider angiomas. There was edema of the ankles (1 +).

Course in the Hospital.—A paracentesis was performed on admission, and 13 quarts (12 liters) of straw-colored ascitic fluid was removed. After this procedure, the liver could be felt 3 finger-

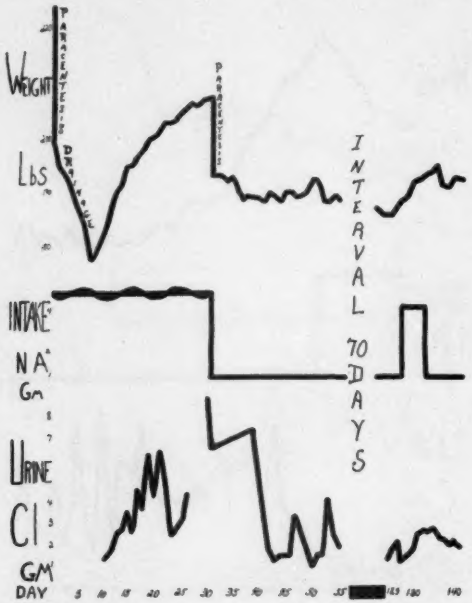

Fig. 4.—Chart showing course in the hospital in case 4 (patient A. A.).

TABLE 4.—*Results of Liver Function Studies in Case 4 (A. A.)*

Hospital Day	1	23	43	71	112	140	156
Albumin, Gm./100 cc.	2.6	3.0	3.3	4.6	3.3	2.6	1.9
Globulin, Gm./100 cc.	2.5	2.9	2.8	2.5	2.2	2.3	2.1
Thymol, units	7	...	2	3	2	...	...
Bilirubin, mg./100 cc.	1.4	...	...	0.5	...	...	...
Prothrombin time, % of normal	27	...	48	...	35	...	...

breadths below the costal margin and the tip of the spleen was palpable. He was given the usual diet high in protein, carbohydrate and calories, with supplementary vitamins but without sodium restriction. However, the ascitic fluid progressively reaccumulated, requiring a second paracentesis one month after admission (fig. 4). After this procedure, he was placed on the special diet with restricted sodium intake. His weight remained essentially stable, and he did not reaccumulate further ascitic fluid. He did not require further paracentesis. Studies of his liver function, however, showed little improvement, as the retention of sulfobromophthalein (bromsulphalein®) sodium remained high and the serum albumin level did not become normal. The superficial dilated veins, however, disappeared.

Comment.—This was a 55 year old alcoholic, with advanced Laennec's cirrhosis, requiring two paracenteses before institution of the special restricted sodium regimen. After sodium restriction, no reaccumulation of ascitic fluid occurred and no further paracenteses were needed, although the results of the patient's liver function tests remained poor.

CASE 5.—A. B., a 54 year old Portuguese man, had a history of alcoholism of 20 years' duration and had noted ankle edema and progressive swelling of the abdomen.

There was past history of syphilis in 1919, which was treated at that time. The family history was essentially noncontributory.

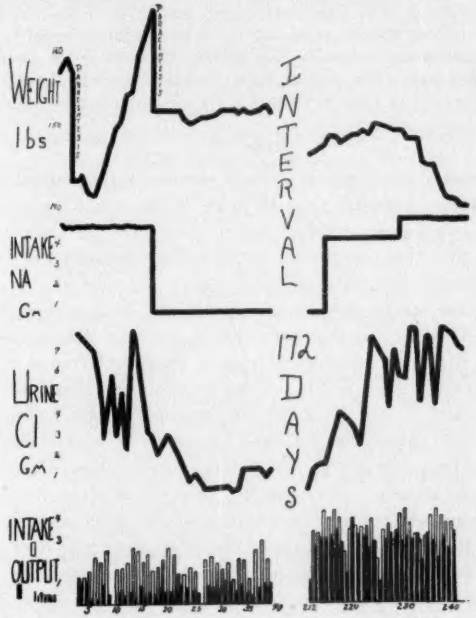

Fig. 5.—Chart showing course in the hospital in case 5 (patient A. B.).

TABLE 5.—*Results of Liver Function Studies in Case 5 (A. B.)*

Hospital Day	1	28	40	69	90	134	170	200	236	240
Albumin, Gm./100 cc.	2.6	2.8	3.3	2.9	3.7	3.1	4.1	3.5	4.2	3.4
Globulin, Gm./100 cc.	3.3	3.1	3.0	3.6	2.9	2.4	2.9	3.5	2.1	3.2
Thymol, units	14	10	17	18	14	9	9	10	7	5
Bilirubin, mg./100 cc.	2.8	2.4	1.9	2.3	2.3	1.9	2.2	2.2	1.5	1.4
Prothrombin time, % of normal	52	40	52	55	46	52	52	41	45	..

Physical examination revealed a well developed, fairly well nourished negroid man. The scleras showed icterus. The abdomen was greatly distended with fluid. Prominent dilated veins were present on the anterior abdominal wall. There was pitting edema of the legs (2 +).

Course in the Hospital.—Paracentesis was performed shortly after admission. For three days considerable ascitic fluid drained from the puncture wound. When drainage ceased, rapid reaccumulation of fluid took place, with a gain in weight (fig. 5) from 142 to 165 pounds (64.4 to 74.8 Kg.). A second paracentesis was performed at that time, after which he was placed on the special diet. No further increase in ascitic fluid took place, although he continued

to have a mild amount. His sodium intake was increased on his two hundred and fourteenth hospital day by addition of 4 Gm. of sodium chloride in enteric-coated® tablets. No increase in the ascitic fluid of significance was noted. On the two hundred and twenty-eighth hospital day the amount of sodium chloride was increased to 6 Gm. After this, prompt loss of the greater part of residual ascitic fluid took place, with loss in weight of 10 pounds (4.5 Kg.). He was discharged with a minimal amount of fluid and without edema. Follow-up observation two months later showed no significant change. His liver and spleen were palpable at the costal margin.

He was readmitted shortly thereafter in a comatose state with mild gastrointestinal bleeding and died after development of several generalized convulsions. Autopsy study revealed 600 cc. of fluid in abdomen, 2,000 cc. in the right pleural cavity and 120 cc. in the left. His liver weighed 900 Gm. and was extremely fibrotic, presenting the picture of far advanced Laennec's cirrhosis. The portal venous system and collaterals were dilated. No lesion of the central venous system was demonstrable on the gross pathological study. Results of the liver function tests done were not significantly different from those at the end of his previous admission (table 5).

RESULTS

During the initial control period without sodium restriction, all patients showed further accumulation of ascitic fluid in spite of the usually accepted therapeutic dietary regimen with supplementary vitamins. In three the accumulation required paracentesis. In the other two the restricted sodium regimen was begun at a point that paracentesis was imminent.

Institution of the special diet containing 605 mg. of sodium resulted in control of the problem of ascites, so that paracentesis was not then necessary in any of the patients. In the three who had previously required removal of intraperitoneal fluid by trocar (cases 1, 4 and 5), the degree of ascites remained stationary. In the other two (cases 2 and 3) in whom paracentesis was imminently required, restriction of sodium intake was followed by a rapid loss of ascitic fluid.

The results of liver function studies (tables 1 to 5) showed consistent improvement in all but one patient. This patient (case 4), in spite of control of ascites, failed to show improvement of his serum albumin level or sulfobromophthalein excretion. This is felt to be indicative of the severe degree of liver disease present.

The special diet was terminated in three of the patients while they were still under observation. After loss of his ascitic fluid, one patient (case 2) was returned to the control period diet. Reaccumulation of fluid did not take place, indicating that he had regained the ability to excrete sodium and water in a more normal fashion. The others (cases 4 and 5) were given sodium chloride in enteric-coated® tablets at a time that their ascites had been stabilized for a number of weeks. Their responses were greatly dissimilar. In the one (case 4) there was a prompt increase in weight and accumulation of ascitic fluid. His urinary chloride excretion was essentially unchanged, indicating that the administered sodium chloride was retained in the body.

The third patient (case 5), on the other hand, in whom the ascites had been stable at a moderate level for 7½ months, sustained a diuresis with loss in weight of 10 pounds and the remainder of his ascitic fluid. Coincident with this was a notable rise in the urinary excretion of chloride. This response was felt to indicate that during the period of sodium restriction his total body sodium had reached a low level. Perhaps conservation of salt and water was due to the reduced level rather than to the original defect in sodium excretion associated with his cirrhosis. During the treatment period the patient's liver disease had improved, and

his body had regained its ability to excrete salt and water in a normal fashion. This, however, may not have occurred because of renal conservation of salt and water in the presence of sodium deficit. The administration of sodium chloride may have overcome the deficit and allowed for diuresis. This is largely conjecture, as the facilities for measuring sodium directly were not available to us.

Coincident with control of ascites and improvement in liver function, the visible evidence of portal collateral circulation diminished in all patients. This was striking in patient E. F. (case 3), in whom the dilated veins were so prominent on admission.

COMMENT

The control of ascites is an important problem in the management of Laennec's cirrhosis of the liver. Repeated paracenteses are a considerable source of protein loss to the patient. In fact, the formation of ascitic fluid itself is a form of internal plasmapheresis and can be considered an actual loss to the body before mechanical removal of the fluid by trocar. Therapy directed toward the control of the peritoneal transudation is, therefore, an essential part of the treatment of cirrhosis.

In considering the mechanism of ascites, it is only reasonable to begin with local factors in the liver and its vascular system. Regardless of emphasized general fluid disturbances of the body in cirrhosis, the fact remains that fluid accumulates to the greatest extent in the peritoneal cavity rather than simply in the dependent parts of the body.

Increased Hydrostatic Pressure.—Increased hydrostatic pressure in the portal veins is a common finding in cirrhosis.[4] The cause of portal hypertension has been thought to be the increased fibrous tissue acting as a mechanical obstruction to portal flow through the liver. However, even superficial consideration makes it clear that it is not mechanical scar tissue alone which determines formation of ascitic fluid. The rapid improvement sometimes seen with treatment is not consistent with a stationary defect of this type. Biopsies have shown, in addition, no correlation of ascites with the degree of scarring present.[5] A dynamic circulatory process must exist with a background of diseased liver cells. Perfusion studies of cirrhotic livers have shown interesting results. Dock [6] observed that perfusion of the cirrhotic liver at postmortem examination through the portal vein alone did not reveal as great an obstruction to flow as anticipated. However, simultaneous perfusion of the liver by the hepatic artery and the portal vein resulted in greatly restricted flow in the portal vein. This indicated anastomosis of the hepatic arterial and the portal venous beds in the sinusoids of the liver. Such anastomotic connections have been demonstrated anatomically.[7] We feel that in the presence of disease of the liver cells there may be increased flow from the hepatic arterioles through these anastomotic connections. This, in turn, might act to impede portal

4. Rousselot, L. M.: Congestive Splenomegaly (Banti's Syndrome), Bull. New York Acad. Med. **15**:188 (March) 1939.

5. Post, J., and Rose, J. V.: Clinical, Functional and Histological Studies in Laennec's Cirrhosis of the Liver, Am. J. Med. **8**:300 (March) 1950.

6. Dock, W.: Shattuck Lecture: The Clinical Significance of Some Peculiarities of the Circulation in the Kidneys, Liver, Lungs, and Heart, New England J. Med. **236**:773 (May 22) 1947.

7. Knisley, M. H., in Liver Injury: Transactions of the Fifth Meeting, Sept. 26 and 27, 1946, New York, Josiah Macy, Jr., Foundation, 1947, pp. 21-41.

venous flow and result in a great rise in the hydrostatic pressure of the portal vein. Indirect evidence is the associated disappearance of the visible collateral circulation seen with improvement in liver function. The effect of increased portal venous pressure, in accordance with Starling's hypothesis, favors transudation into the peritoneal cavity. However, the problem of ascites is not explained completely by simple portal hypertension. It seems clear that ascites does not always follow portal hypertension even sufficient to cause development of collateral circulation of a considerable magnitude. This suggests that the factor may be one of degree or may be influenced by the presence of other factors which overcome compensatory mechanisms.

Hypoalbuminemia.—Lowered serum albumin is a common finding in cirrhosis.[8] Ascites has been related to the lowered colloid osmotic pressure of the serum.[8] However, studies have shown that the level of serum albumin is not the controlling factor.[9] There is instead a complex balance of forces at the level of the capillaries of the portal vascular system. Two forces favor ascitic fluid formation. These are the hydrostatic pressure in the portal vein and the colloid osmotic pressure of the ascitic fluid itself. Against these are the colloid osmotic pressure of the plasma and the hydrostatic pressure of the ascitic fluid. It has been shown that a dynamic osmotic equilibrium exists between the plasma and the ascitic fluid and that the difference between the colloid osmotic pressure of the plasma and that of the ascitic fluid remains constant.[10] Ascites is accompanied with diffusion of serum protein into the peritoneal cavity, and fluid diffuses from the plasma into the ascitic fluid to readjust the osmotic equilibrium.

The reduction of oncotic pressure by hypoalbuminemia plays a part in ascites, but its role is variable. With the portal hypertension, it may allow for leakage of protein from the portal capillaries into the peritoneal cavity. Once ascites is begun and established, the osmotic laws are followed as outlined.

Salt and Water Retention.—Interest has shifted recently away from the action of the capillary membrane toward that of the kidney in states of edema. Experimental ascites produced by constriction of the inferior vena cava can be made to vary directly with sodium intake.[11] By increasing the salt intake, the ascitic fluid was made to increase. Conversely, restriction of sodium decreased the ascites. Patients with cirrhosis frequently have oliguria and extremely low sodium excretion in spite of usual intake in the diet.[12] This is especially true of those accumulating ascitic fluid. In the patients who are improving and not accumulating fluid, the sodium and water excretion is within normal limits. It seems clear that the

8. Post, J., and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: Relation to Prognosis and to Formation of Ascites, Arch. Int. Med. **69**:67 (Jan.) 1942.

9. Ralli, E. P.; Robson, J. S.; Clark, D., and Hoagland, C. L.: Factors Influencing Ascites in Patients with Cirrhosis of the Liver, J. Clin. Investigation **24**:316 (May) 1945.

10. Mankin, H., and Lowell, A.: Osmotic Factors Influencing the Formation of Ascites in Patients with Cirrhosis of the Liver, J. Clin. Investigation **27**:145 (Jan.) 1948.

11. McKee, F., and others: Protein Metabolism and Exchange as Influenced by Constriction of the Vena Cava: Experimental Ascites and Internal Plasmapheresis, Sodium Chloride and Protein Intake Predominant Factors, J. Exper. Med. **87**:457 (June) 1948.

12. Post and Patek.[8] McKee and others.[11] Farnsworth, E., and Krakusin, J. S.: Electrolyte Partition in Patients with Edema of Various Origins: Qualitative and Quantitative Definition of Cations and Anions in Hepatic Cirrhosis, J. Lab. & Clin. Med. **33**:1945 (Dec.) 1948.

retained sodium and water in decompensated cirrhosis is utilized in the formation of ascitic fluid. It has been found that restriction of sodium intake to about 1 Gm. daily prevents this process from continuing and results in no further accumulation of fluid.[2b] This enables a dietary treatment to be effective, as no further removal of protein by paracentesis is needed. After sufficient improvement occurs and the disease processes diminish, the body again is able to excrete normal amounts of sodium and water, but not all patients regain this ability. That the body should retain sodium and water in cirrhosis with ascites when the extracellular compartment is already flooded is an incongruous situation. A possible mechanism has already been mentioned. As serum protein passes into the peritoneal cavity, the osmotic equilibrium between the plasma and ascitic fluid is upset. The ascitic fluid becomes hypertonic to the plasma, and fluid shifts from the plasma to the ascitic fluid. The loss of fluid from the circulation is perhaps the stimulus for retention of water and salt by the kidneys.

Antidiuretic Hormones.—Ralli [9] has found increased antidiuretic substances in the urine of patients with ascites. It has been postulated that the increased hormone is due to lack of inactivation by the liver. Increased hormone has been found also in states of dehydration.[13] It is, therefore, a question whether the increased hormone is a cause or an effect.

SUMMARY

The accumulation of ascitic fluid is due to a number of factors, some of these local at the level of the capillaries in the portal system and some general, such as salt and water retention.

Therapeutically one may directly influence the fluid and electrolyte disturbance, whereas the local factors can be influenced only indirectly by a program which improves the disease itself.

Five patients are presented in whom the ascites was controlled over a period of several months by restricted sodium intake. Dietary management without consideration of this factor proved ineffective in the control of ascites.

After control of the ascites readministration of sodium gave variable results.

13. Peters, J.: The Role of Sodium in the Production of Edema, New England J. Med. **239**:353 (Sept. 2) 1948.

TREATMENT OF ULCERATIVE COLITIS AND REGIONAL ENTERITIS WITH ACTH

Significance of Fecal Lysozyme

SEYMOUR J. GRAY, M.D., Ph.D.
ROBERT W. REIFENSTEIN, M.D.
JOHN A. BENSON Jr., M.D.
AND
J. C. GORDON YOUNG, M.D.
BOSTON

THE BENEFICIAL effects induced by pituitary adrenocorticotropic hormone (ACTH) treatment on a wide variety of systemic diseases involving mesenchymal tissue, or in which an antigen-antibody type of reaction may be implicated, suggested the use of the substance in the treatment of chronic nonspecific ulcerative colitis. The study was stimulated further by the relationship of chronic stress and the general adaptation syndrome to ulcerative colitis and the significant incidence of polyarthritis and extensive secondary mesenchymal involvement of the colon in this disease.

The immediate and long term effects of ACTH administration on the clinical course of six patients with ulcerative colitis and on that of two patients with regional enteritis have been evaluated over a period of 16 months, and the clinical response to ACTH therapy was integrated with the fecal lysozyme titer, which is a measure of the activity of the disease process.

SELECTION OF PATIENTS

In view of the spontaneous remissions which may occur in these disease syndromes, ACTH treatment was administered only to patients with severe, extensive ulcerative colitis and regional enteritis in the acute phase of the diseases. All these patients were completely incapacitated by their disease and had not responded to an adequate control period (one to four months) of good medical management, which included treatment with antibiotics and detergents, prolonged rest in bed, regulated diet, blood transfusions and the usual supportive therapy.

The activity of the disease was manifested by fever, leukocytosis, anemia, anorexia, profound weight loss, abdominal pain, tenesmus and intractable grossly bloody

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Dr. Gray is Assistant Professor of Medicine. Drs. Benson and Young are Research Fellows in Medicine. Dr. Reifenstein is Assistant in Medicine and Postdoctorate Research Fellow of the United States Public Health Service.

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From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine and the Biophysical Laboratory, Harvard Medical School.

diarrhea (eight to 15 evacuations daily). The sigmoidoscopic examination demonstrated diffusely ulcerated, freely bleeding, friable mucosa in all patients with ulcerative colitis, and the roentgen studies revealed extensive involvement of the colon and rectum in all but one patient.

The patients with regional enteritis were also acutely ill and presented the characteristic picture of the disease on roentgenologic examination.

TREATMENT

Every effort was made to eliminate the psychotherapeutic effects associated with a new form of treatment. The patients were not informed of the change in medication and were given parenteral placebos before ACTH therapy was begun. A moderately unrestricted bland diet was maintained unchanged throughout the control and treatment periods. All medication, except use of phenobarbital, was discontinued during the period of ACTH administration.

ACTH was given in doses of 20 to 40 mg. intramuscularly at six hour intervals for periods of four to eight weeks, depending on the requirements and clinical response of the individual patient. The dose of ACTH was reduced gradually at the end of the period of treatment. All patients were maintained on a limited salt and fluid intake and were given 0.9 Gm. of potassium chloride three times daily.

Laboratory studies included determinations of the blood eosinophil count [1] and urinary ketosteroids, as well as of the sedimentation rate, serum proteins, fasting blood sugar, blood carbon dioxide, serum chlorides, hematocrit, hemoglobin concentration and white cell count.

The consistency, appearance and number of stools were recorded daily, and the stools were analyzed for occult blood. The appearance of the colon was studied by repeated proctosigmoidoscopic examination and roentgen visualization with barium sulfate enemas. The fecal lysozyme titer [2] was determined at frequent intervals prior to, during and following ACTH therapy.

RESULTS

The administration of ACTH resulted in a significant and often dramatic remission in the acute aspects of the disease in five of the six patients with ulcerative colitis and in the two patients with regional enteritis. The remission was manifested by a notable decrease in the diarrhea, disappearance or diminution of blood in the stools, improvement of the appearance of the mucosa on sigmoidoscopic examination, relief of abdominal pain and tenesmus, prompt fall in temperature, sedimentation rate and fecal lysozyme titer and an increase in appetite and weight, accompanied with a sense of well-being.

Diarrhea.—The persistent, unrelenting diarrhea, which constitutes one of the most serious problems in these patients, diminished significantly within the first week of treatment in most patients and was brought under excellent control within two weeks if the dosage of ACTH was adequate.

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1. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: The Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005 (July 17) 1948.

2. Meyer, K., and Hahnel, E.: The Estimation of Lysozyme by a Viscosimetric Method, J. Biol. Chem. **163**:723, 1946.

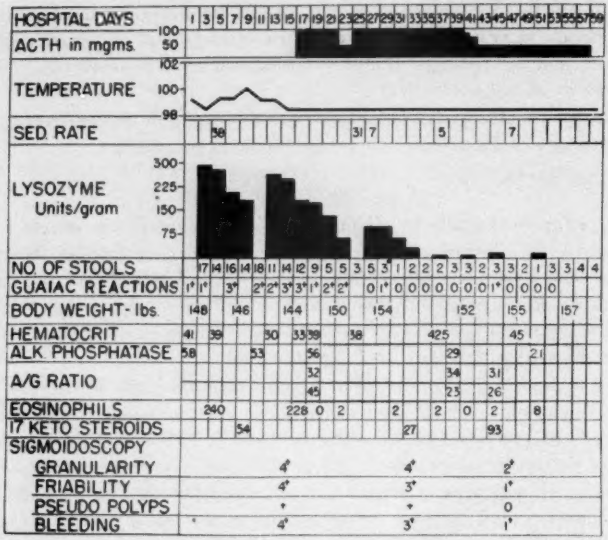

Fig. 1.—Effect of ACTH treatment on ulcerative colitis in patient O. D. Asterisk indicates appearance of formed stools on day noted and thereafter.

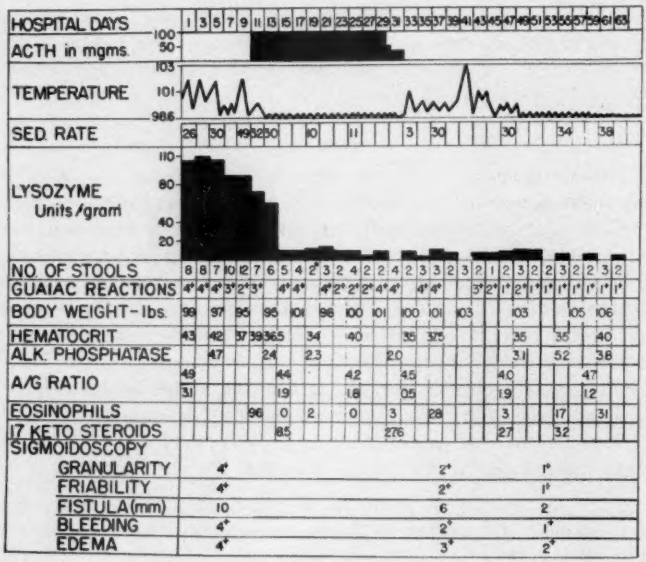

Fig. 2.—Effect of ACTH therapy on ulcerative colitis in patient B. F. Asterisk indicates appearance of formed stools on day noted and thereafter.

Patient O. D., a 46 year old man, for example, complained of fecal incontinence for four months, intractable diarrhea with 10 to 18 blood-stained, watery evacuations daily, associated with severe tenesmus, abdominal pain, a low grade fever and a 25 pound (11.3 Kg.) weight loss (fig. 1) in spite of prolonged hospitalization and intensive medical therapy, including use of detergents and antibiotics and psychotherapy.

Within one week of ACTH treatment (100 mg. daily) the number of evacuations decreased to five semiformed stools daily, and by the end of the second week the patient was passing one to three formed stools daily which were free of occult blood. This was the first time in four months that a formed stool was observed.

The tenesmus and abdominal pain diminished greatly within the first week and completely disappeared at the end of the second week of treatment. The characteristic euphoria and increase in appetite were noted soon after therapy was instituted, and the patient gained 10 pounds (4.5 Kg.) within one month.

TABLE 1.—*ACTH Therapy in Ulcerative Colitis and Regional Enteritis*

Patient	ACTH Treatment		Results	Relapse	
	Days	Mg./Day		Severity*	Time from ACTH Therapy
		Ulcerative Colitis			
O. D.	26	100	Excellent	0	16 mo.
	16	40			
A. M.	24	80	Good	++	18 wk.
	16	100	Good	0	8 mo.
B. F.	21	100	Good	++	9 mo.
E. G.	18	80	Excellent	++++	21 days
	14	Cortisone, 200			
	14	ACTH, 120	Fair		
O. H.	11	80	Good		
	22	160	Good	0	8 wk.
B. O.	15	ACTH, 100			
	14	Cortisone, 200	No effect		
		Regional Enteritis			
H. E.	21	160	Good	++	1 mo.
I. N.	21	80	Excellent	++	1 mo.
	21	100	Excellent	++	1 wk.

* Zero indicates no relapse occurred up to time specified. Plus signs indicate seriousness of relapse.

These clinical changes were paralleled by a decided fall in the sedimentation rate and a rise in the hematocrit.

A similarly effective control of diarrhea was observed after 14 to 18 days of ACTH therapy in patient B. F. (fig. 2), who presented the additional problem of a large perianal fistula, which decreased rapidly in size on treatment.

Two additional patients with previously intractable diarrhea of four to six months' duration responded satisfactorily within 14 to 16 days of ACTH administration (E. G. and O. H., table 1).

The clinical improvement was definite but less dramatic in patient A. M. (fig. 3), although the nocturnal diarrhea disappeared within two weeks of therapy in spite of a rectal stricture and persistent symptoms of five months' duration.

No clinical response whatever was observed in one patient with chronic ulcerative colitis of 23 years' duration, extensive fibrosis and cicatrization of the colon, multiple strictures and perianal and perineal fistulas (B. O., table 1) who was treated during an acute, severe exacerbation.

ACTH therapy appeared to induce a satisfactory remission in the two patients with regional enteritis. A dramatic improvement was observed in patient I. N. (table 1), a 27 year old man with a history of watery diarrhea (eight to 10 evacuations daily), severe abdominal pain and a 35 pound (15.9 Kg.) weight loss of 10 weeks' duration. Roentgenograms revealed extensive involvement and fixation of the terminal portion of the ileum. A previous surgical exploration had established the same diagnosis.

The patient's course was progressively downhill, in spite of intensive therapy with antibiotics, diet, blood transfusions, fluids parenterally and sedation. He continued to lose weight and complained of severe, intractable, cramping abdominal

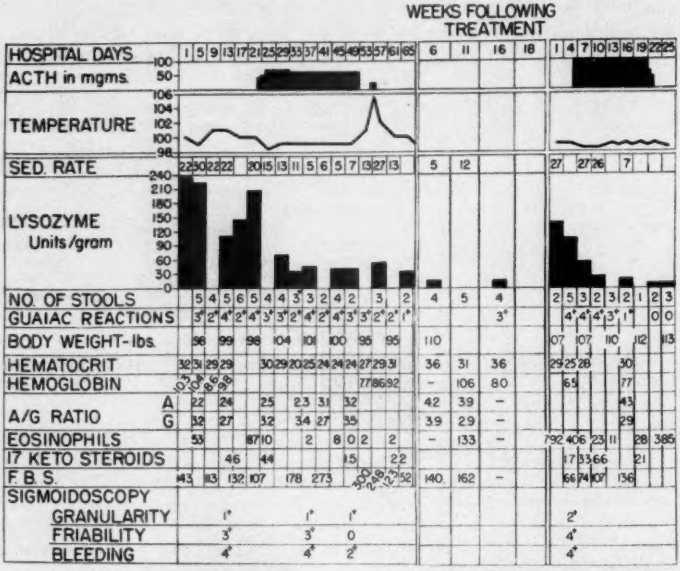

Fig. 3.—Effect of ACTH treatment on ulcerative colitis in patient A. M., showing a remission and relapse of the disease paralleled by a fall and rise in the lysozyme titer. Asterisk indicates appearance of formed stools on day noted and thereafter. Values listed after F. B. S. are fasting blood sugar levels.

pain, nausea and vomiting. The abdominal examination revealed diffuse tenderness and involuntary rigidity.

Within the first three to four days of ACTH therapy, the heretofore intractable abdominal pain was completely relieved and the stools became formed for the first time in three months. The patient displayed a striking euphoria, and his appetite became ravenous. Within three weeks of ACTH therapy, the patient gained 27 pounds (12.2 Kg.) and averaged two formed bowel movements daily which were free of occult blood. There was no significant change, however, in the roentgenologic appearance of the terminal part of the ileum after ACTH therapy. A similar but less dramatic clinical improvement was observed in patient H. E. (table 1).

Gross and Occult Blood in Stools.—As the diarrhea subsided, there was a concomitant decrease in both the gross and the occult blood in the stools within one to two weeks of therapy. The reaction to the guaiac test for occult blood was negative within one week in patients O. D. (fig. 1) and E. G., in whom gross blood had been present consistently for four months previously.

Macroscopic blood in the excreta disappeared within the first two weeks of ACTH therapy in patients B. F. (fig. 2) and A. M. (fig. 3), but occult blood persisted for approximately eight to 10 weeks after the onset of treatment in B. F. A. M. had evidence of polyps in the transverse colon demonstrable on roentgenogram, and occult blood never disappeared throughout the eight month period of observation.

A similar diminution of gross and occult blood in the stools was observed within two weeks of ACTH therapy in both patients with regional enteritis although occult blood was present in the stools of H. E. consistently.

Sigmoidoscopic Appearance of Mucosa.—In general, there was little or no improvement in the sigmoidoscopic picture until the end of three weeks of treatment, although clinical evidence of remission was obvious within two weeks. There appeared to be a lag between the clinical and the sigmoidoscopic reflection of the disease process, with definite and sometimes dramatic evidence of remission appearing on sigmoidoscopy. The mucosa was distinctly less friable, and the bleeding and granularity were greatly diminished. Pinpoint bleeding and diffuse ulceration were, in some instances, spectacularly decreased. In one patient the mucosa appeared essentially normal except for evidence of fine granularity after three weeks of treatment (E. G.). In no instance did the mucosa revert to normal completely, however.

Definite improvement was observed in O. D. (fig. 1) after three weeks of treatment, although minor residual granularity and bleeding were still present. A small single inflammatory pseudopolyp seen on two occasions in the rectal mucosa had disappeared. Six months later the mucosa was indistinguishable from normal.

Less marked but definite improvement was observed in patients B. F. and A. M. after three weeks of treatment. In addition to the mucosal improvement (patient B. F.) a painful, draining perianal fistula 10 mm. in diameter had decreased to 6 mm. and was no longer painful but remained tender on pressure. Three weeks later the fistula was 2 mm. in diameter, and further improvement in the sigmoidoscopic appearance was observed, although the rectal mucosa was still moderately friable and granular, with pinpoint bleeding (fig. 2).

The stricture noted during the examination of patient A. M. persisted, although it appeared less edematous.

There was no improvement in the appearance of the mucosa of patient B. O., which displayed multiple strictures, polyps and fistulas in spite of prolonged treatment with ACTH and cortisone (table 1).

Roentgenologic Appearance.—Diminution of spasm, irritability and intestinal motility were demonstrated in one patient with regional enteritis (H. E.), although the involved portion of the ileum was still extremely abnormal after therapy. An increase in the caliber and length of the colon, an increase in haustral markings and a more normal mucosal pattern were demonstrated in two other patient (B. F. and O. D.), although the serration persisted.

There was no significant change in the roentgen appearance of the colon or ileum after ACTH therapy in the remaining patients, except for diminution of spasm and irritability.

Fecal Lysozyme.—Lysozyme, a mucolytic enzyme present in the colonic mucosa and other tissues in the body, has been proposed as an etiological agent in the pathogenesis of ulcerative colitis in view of the high titer found in the stools of patients suffering from this disease. It has been postulated that lysozyme removes the protective surface mucus from the colon and thus favors ulceration of the denuded mucosa by proteolytic enzymes.[3]

Studies in our laboratory revealed a consistently high fecal lysozyme titer during the acute phase of ulcerative colitis and a low value during the chronic inactive or remission phase.[4] The mean lysozyme titer in the present patients was 109 units per gram during the acute phase, decreasing to 12 units during the remission period, compared with the average normal of 4 units (table 2). The fecal lysozyme titer was only slightly elevated in the patients with regional enteritis; the mean value in this group was 8 units per gram.

TABLE 2.—*Summary of Fecal Lysozyme Determinations*

	Number of Cases	Mean Lysozyme Titer, Units/Gram
Normal	21	4
Nonspecific ulcerative colitis		
Acute	11	109
Chronic	19	12
Diarrhea	9	4
Regional enteritis	6	8

A profound fall in the fecal lysozyme titer occurred within four to 17 days of ACTH treatment and coincided with the clinical improvement of the patients. This was observed uniformly in the five patients with ulcerative colitis who responded to ACTH therapy. In B. F., for example, the fecal lysozyme titer decreased from a mean level of 97 units before treatment to 9 units within four days of ACTH therapy (fig. 4).

The decrease in fecal lysozyme titer following ACTH therapy was more gradual but no less impressive in patient O. D. and likewise paralleled the clinical course, diminishing from the pretreatment levels of 291 units per gram to the chronic inactive level of 7 units on the twentieth day of ACTH therapy.

The response of patient A. M. differed from that of the others in that the lysozyme titer did not fall to the remission level until six weeks had elapsed, although there was a partial decrease within 10 days of treatment (fig. 3). This slow lysozyme response was accompanied with a delay in the clinical response and less impressive evidence of improvement on sigmoidoscopic examination.

3. Meyer, K.; Gellhorn, A.; Prudden, J. F.; Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease: II. Lysozyme Activity in Chronic Ulcerative Colitis, Am. J. Med. **5**:496, 1948.

4. Gray, S. J.; Reifenstein, R. W.; Connolly, E. P.; Spiro, H. M., and Young, J. C. G.: Studies on Lysozyme in Ulcerative Colitis, Gastroenterology **16**:687, 1950.

As the disease became quiescent with ACTH therapy, the fecal lysozyme fell from 220 units during the acute phase before treatment to 13 units during the remission. With the recrudescence of the disease 18 weeks later, the lysozyme titer rose again to 110 units and fell to 10 units after the second course of ACTH treatment and the resulting second remission 14 days later (A. M., fig. 3).

An identical parallelism between lysozyme titer and the activity of the disease was observed in E. G. The fecal lysozyme fell from the initial value of 86 units per gram before ACTH therapy to 21 units per gram after three days of treatment, associated with an excellent remission, but increased again to 120 units per gram with a second exacerbation 21 days later.

Reactive mucosal tissue must apparently be present to give a lysozyme response, as patients completely incapacitated by extensive cicatrization of the bowel may reveal normal or only moderately elevated titers. These patients evidently possess insufficient actively functioning colonic mucosa to secrete lysozyme or to respond to therapy. Patient B. O. (table 1), for example, presented fecal lysozyme

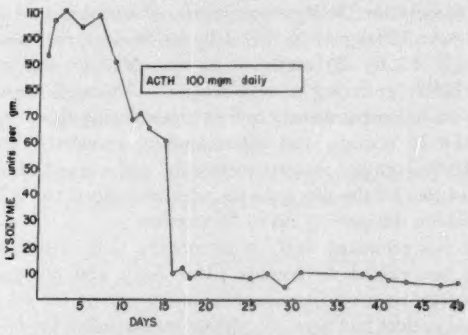

Fig. 4.—Effect of ACTH administration on fecal lysozyme in patient B. F.

titers ranging from 4 to 45 units before treatment with ACTH and cortisone. There was no lysozyme fall and no clinical or sigmoidoscopic improvement.

Anorexia.—The profound anorexia and weight loss characteristically observed in patients with ulcerative colitis present a serious problem. ACTH administration uniformly produced a consistent and striking increase in the appetite and sense of well-being, which was frequently the turning point in the remission in these malnourished, dehydrated patients.

There was a definite gain in weight within the first three weeks of therapy, which continued for many weeks and months thereafter in all the patients. Although some of the initial weight gain was probably due to retention of fluid, the long term increase after ACTH therapy was discontinued unquestionably represented a true weight gain.

Systemic Improvement.—The disappearance of fever, fall in sedimentation rate and increase in hematocrit, plasma proteins and body weight were observed quite consistently, the fall in temperature and sedimentation rate occurring dramatically within a few days of therapy.

LONG TERM FOLLOW-UP OBSERVATIONS

Definite relapses occurred three weeks to nine months following the discontinuation of ACTH therapy in three of the patients with ulcerative colitis and in both patients with regional enteritis. The relapses were relatively mild in all but one patient (E. G.).

Patient A. M. (fig. 3) had a mild recurrence of grossly bloody diarrhea 18 weeks following ACTH therapy and responded satisfactorily to a second course of treatment. She has remained essentially asymptomatic without relapse for eight months and gained 35 pounds in weight; occult blood in the stools and anemia persisted, however. Proctoscopy revealed a healed, inactive ulcerative colitis with some thickening of the mucosa and fine granularity, but no friability or gross bleeding. The persistent blood loss was caused by polyps in the transverse colon demonstrable on roentgenogram.

A severe relapse following prolonged physical exertion occurred 21 days after ACTH treatment was discontinued in E. G., who had previously experienced an excellent and dramatic response to ACTH therapy. A course of treatment with cortisone, 200 mg. daily for 14 days, was instituted and appeared ineffective. The patient was then given 120 mg. of ACTH daily for 14 days, with some improvement.

One patient (B. F., fig. 2) remained in remission for nine months following ACTH therapy before suffering a mild relapse. Although there were transient episodes of diarrhea following dietary indiscretions during this 9 month period, the patient had gained 25 pounds, and sigmoidoscopy revealed a thickened, healed, slightly friable, finely granular mucous membrane and a small persistent fistula.

The disease of two of the five patients who responded to ACTH therapy has remained in remission for periods up to 16 months.

Patient O. D. has remained well for 16 months, is on a full, unrestricted diet, works regularly, has gained 40 pounds (18.1 Kg.) and presents an essentially normal rectal mucosa on proctoscopic examination except for mild thickening and granularity. This patient had been completely incapacitated for seven months prior to treatment.

Both patients with regional enteritis had mild recurrences of diarrhea one month after ACTH administration was discontinued. Patient I. N. (table 1) was given a second course of ACTH therapy and responded promptly with an excellent remission and a weight gain of 30 pounds (13.6 Kg.).

COMMENT

Any discussion of therapy in ulcerative colitis must take serious cognizance of the spontaneous remissions and exacerbations which characterize this disease. In view of the selection of patients and careful control studies, however, the evidence indicates that treatment with ACTH induced a remission or greatly accelerated its appearance in five of the six patients who were completely incapacitated by their disease and were refractory to any other form of medical management.

The frequent relapses which occur after adequate therapy and the failure of the mucous membrane to return completely to normal on sigmoidoscopic examination emphasize the fact that use of ACTH does not produce a cure of the disease. The dramatic effect obtained in one patient whose colitis appears to be in permanent remission 16 months after treatment is encouraging (patient O. D., table 1), but

similar results may occur spontaneously without specific therapy. The second patient (O. H.) who has not experienced a relapse is working for the first time in six months and is free of symptoms, although the mucosa retains some residual evidence of activity on sigmoidoscopy. A longer follow-up period is necessary to evaluate the significance of these remissions.

The patients with ulcerative colitis and regional enteritis who experienced relapses responded exceedingly well to a second course of therapy. In all patients but one (E. G.) the relapse was mild. There may be a good rationale for long term maintenance therapy or repeated courses of treatment.

In the presence of extensive fibrosis and diffuse cicatrization, a satisfactory response to ACTH therapy may not be anticipated, as was demonstrated in patient B. O. The best results may be obtained in the early stages of the disease before complications of strictures, polyps and fistulas result, although patients B. F. and A. M. experienced a good remission with ACTH treatment in spite of these additional hazards.

The sense of well-being and increase in appetite which result from ACTH administration are of incalculable value in the treatment of these debilitated, malnourished patients. The increased appetite may be the result of an increase in the gastric secretion of acid and pepsin produced by ACTH [5] or the diminution in the systemic manifestations of infection resulting from ACTH administration. What part these nonspecific effects have in the remission of the disease remains to be determined.

The remission induced by use of ACTH offers an additional supportive measure in the preparation of patients for surgical treatment if ileostomy should become necessary.

The possibility of ileostomy was considered during the second admission of E. G., who presented the problem of fulminating ulcerative colitis with massive hemorrhage and profound weight loss. The prompt effect of ACTH therapy in the control of diarrhea and blood loss obviated the necessity for ileostomy but left the distinct impression that the patient was a considerably better risk for this procedure as a result of treatment.

The duration of ACTH treatment and the dosage are extremely important factors in determining the eventual clinical response. The longest remission was observed in patient O. D., who was treated for 42 days (table 1; fig. 1), while the shortest remission and the severest relapse were experienced by patient E. G., who received treatment for only 18 days. The optimum period of therapy is probably three to six weeks, with daily doses of 80 to 160 mg., depending on the individual patient.

The dose requirement does not appear to be related to the age or weight of the patient or the severity of the disease. In some instances (patients E. G., O. H., H. E.; table 1) there was no demonstrable clinical response to 80 to 100 mg. of ACTH daily, although the eosinophil fall and urinary 17-ketosteroid response were

5. Gray, S. J.; Spiro, H. M., and Reifenstein, R. W.: ACTH and Gastrointestinal Enzymes, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 137; ACTH and Gastrointestinal Enzymes, Bull. New England M. Center **12**:169, 1950.

satisfactory. When the dose was increased to 120 to 160 mg. daily, the clinical effect was apparent immediately. The final decision regarding dosage and duration of therapy depends on the clinical response.

The complications of ACTH therapy consisted of a temporary increase in the fasting blood sugar level to 300 mg. per 100 cc. in one patient (A. M., fig. 3) within two weeks of ACTH administration, with return to normal levels 14 days after the medication was discontinued. This patient also had sterile subcutaneous abscesses, a virus pneumonia, fever and hyperkalemia on discontinuation of ACTH therapy. These complications did not appear to affect the colitis adversely and responded satisfactorily to antibiotic and corrective therapy.

Other complications were moderate hirsutism, acne and pigmentation, which gradually disappeared after ACTH treatment was terminated (B. F., fig. 2).

Roundness of the face was observed in all patients during the second to third week of treatment. This varied in degree and diminished gradually after discontinuation of therapy.

Fever immediately following the termination of ACTH therapy was observed in B. F. (fig. 2) and probably represented an exaggerated withdrawal effect. The eosinophil count increased and the urinary 17-ketosteroid excretion fell from 27.6 to 2.7 mg. in 24 hours during the febrile period (fig. 2). No flare-up of the colitis resulted, however, and the temperature returned to normal without additional treatment within two weeks.

The fecal lysozyme titer parallels the clinical course of ulcerative colitis, decreasing with remissions and increasing with exacerbations. It is a good measure of the activity of the disease and reflects the tissue response to injury.[4] Granulation tissue[6] and exudate,[7] for example, contain significant amounts of lysozyme and constitute tissue reactions to injury. The bacteriolytic properties of lysozyme are in the same category.

The consistent and often dramatic decrease in fecal lysozyme observed in patients responding to ACTH therapy (fig. 4) may reflect the inhibitory effect of ACTH on the tissues' reaction to injury. It follows a pattern similar to that of the diminution or inhibition by ACTH or other tissue reactions to injury and inflammation, such as fibroblastic proliferation, tissue lymphocytes, perivascular exudation, gamma globulin, fibrinogen, complement and hyaluronidase. It is of interest that both hyaluronidase and lysozyme, which are inhibited by ACTH, act on similar mucopolysaccharide substrates.

There is a good possibility that ulcerative colitis patients who do not demonstrate high fecal lysozyme titers in the acute phase of the disease may not respond to ACTH therapy, as was observed in patient B. O., since the lysozyme titer measures both the activity of the disease process and the ability of the tissue to respond to the injury. If there is inadequate functioning mucosa available because of irreversible damage or fibrosis, a therapeutic response to ACTH administration may not follow.

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6. Prudden, J. F.; Lane, N., and Meyer, K.: Lysozyme Content of Granulation Tissue, Proc. Soc. Exper. Biol. & Med. **72**:38, 1949.

7. Prudden, J. F.; Lane, N., and Levison, J.: Lysozyme Titers in Regional Enteritis, Miscellaneous Tissues, Microorganisms and Excreta, Proc. Soc. Exper. Biol. & Med. **72**:220, 1949.

The discussion of lysozyme has been limited to ulcerative colitis, as the fecal lysozyme titer of patients with regional enteritis did not differ appreciably from normal. This may be explained by a specific difference in mucosal response or dilution of the enzyme in transit through the large bowel.

The beneficial effect of the use of ACTH may be attributed, in part, to its ability to decrease the extensive inflammatory reaction of the involved tissues and to diminish the systemic and toxic manifestations of infection. The inhibition of fibroblastic proliferation alone may prove of great value if ACTH can prevent fibrosis and stricture formation, which are among the most serious complications of these disease syndromes.

SUMMARY AND CONCLUSIONS

The administration of pituitary adrenocorticotropic hormone (ACTH) resulted in a significant and often dramatic remission in five of six patients with severe extensive ulcerative colitis who had not responded to an adequate control period of good medical management. Two patients with intractable regional enteritis experienced a similar remission. No response was observed in one patient with a 23 year history of ulcerative colitis and extensive cicatrization of the colon with stricture formation, fistulas and polyposis.

The remission was characterized by a marked decrease in diarrhea, disappearance or diminution of blood in the stools, improvement of the appearance of the mucosa on sigmoidoscopic examination, relief of abdominal pain and tenesmus, prompt fall in temperature and sedimentation rate and an increase in appetite and weight, accompanied with a sense of well-being.

Relapses occurred in three patients with ulcerative colitis and in both patients with regional enteritis within three weeks to nine months after ACTH treatment was discontinued. The relapses were mild in all but one patient, and there was a good response to a second course of therapy. Long term maintenance therapy or repeated courses of treatment may be indicated in some patients. In two of the five patients who responded to ACTH therapy the disease has remained in remission for periods up to 16 months.

The fecal lysozyme titer was found to parallel the course and activity of ulcerative colitis, decreasing with remissions and increasing with exacerbations. The level of fecal lysozyme is a measure of the activity of the disease process and is a significant index of the available functioning tissue and its ability to respond to injury. A profound fall in fecal lysozyme, coinciding with the clinical improvement, occurred uniformly in all patients with ulcerative colitis who responded to ACTH therapy. The decrease in fecal lysozyme following ACTH therapy may represent the inhibitory effect of ACTH on the tissues' response to injury. It is a good index of the patient's response to treatment. In the presence of irreversible fibrosis and cicatrization, the lysozyme titer may be low before ACTH therapy is instituted. No therapeutic response may be anticipated in these cases.

The remission induced by ACTH may prove exceedingly helpful in the preparation of patients with ulcerative colitis for surgical treatment.

The dose requirement and the duration of therapy should be individualized for each patient, depending on the clinical response. The best long term results were obtained in patients receiving a prolonged course of treatment.

Administration of ACTH does not constitute a cure but is a valuable adjunct in the therapy of ulcerative colitis and regional enteritis, particularly in the early stages of the diseases.

REPORT OF CASES

PATIENT O. D.—This 46 year old man was admitted to the Peter Bent Brigham Hospital on Oct. 2, 1949, because of intractable diarrhea with 10 to 15 grossly bloody, watery stools daily, nocturnal incontinence, abdominal pain, tenesmus, weakness, fever, joint pains and a 25 pound weight loss of seven months' duration. These symptoms became progressively worse in the four months preceding admission, despite a prolonged period of hospitalization which included rest in bed, dietary care, use of sedatives, antibiotics and detergents, psychotherapy and other supportive treatment, beginning in July 1949. Ileostomy had been advised in view of his poor response to treatment.

On admission the patient had a low grade fever (elevation in temperature to 100 to 100.5 F.), moderate lower abdominal tenderness and evidence of weight loss. The laboratory studies revealed a hematocrit of 39 per cent, which fell to 33 per cent during the pretreatment period, corrected erythrocyte sedimentation rate of 38 mm. per hour, an eosinophil count of 240 per cubic millimeter and serum albumin of 3.2 Gm. and globulin of 4.5 Gm. per 100 cc. Stools were watery and gave 4 + guaiac reactions for blood. No pathogens could be cultured. Enteric agglutinations gave negative results.

The lysozyme titer varied from 176 to 291 units per gram of stool.

Roentgenograms.—Roentgenography with a barium sulfate enema revealed a small tubelike colon, with a finely irregular outline and little mucosal pattern. The entire colon was involved.

Proctoscopic Examination.—Proctoscopy the day before ACTH therapy was begun showed marked coarse granularity, with pronounced friability of the mucosa, diffuse ulceration and free bleeding with one polypoid excrescence on the anterior wall of the rectum.

Course.—The patient was maintained on a salt-poor, bland, low residue diet for 16 days, with no improvement in the presenting symptoms.

On October 18 ACTH therapy was begun in doses of 25 mg. four times daily at six hour intervals. The patient received 100 mg. of ACTH daily for the next 24 days, after which the dose was reduced gradually to 40 mg. daily for an additional 18 days. There was no change in diet or medication during this period except for the administration of potassium chloride (0.9 Gm. three times daily).

Within two days of treatment there were a decided diminution in the generalized muscular stiffness and joint pains and a dramatic reduction in nocturnal diarrhea, tenesmus and flatulence. At the end of one week, the number of evacuations decreased to five daily and the stools were semiformed for the first time in four months. There was a definite increase in appetite and sense of well-being.

After two weeks of treatment, the patient was passing one to three formed or semiformed stools daily, free of occult blood. The increased appetite and sense of well-being continued. Tenesmus, flatulence, abdominal pain and nocturnal diarrhea disappeared, and the patient gained 8 pounds (3.6 Kg.), some of which probably reflected fluid retention. Proctoscopic examination two weeks after treatment revealed no definite change in the appearance of the mucosa except for slight improvement in friability and bleeding. The pseudopolyp seen previously appeared unchanged. These findings were in distinct contrast to the over-all clinical improvement.

During the 42 days of treatment the patient continued to improve, passed two to three formed or semiformed stools daily, free of occult blood, and gained 13 pounds (5.9 Kg.).

Roundness and fulness of the face were observed on the twenty-first day of treatment.

The fecal lysozyme fell from 264 units per gram before treatment to 65 units within one week and continued to fall to 7.5 units on the twentieth day of therapy.

Within one week of treatment, the sedimentation rate fell from 38 to 7 mm. per hour and the hematocrit returned to normal by the third week. The eosinophil count fell from 240 per cubic millimeter to 0 within 24 hours, and the 24 hour urinary 17-ketosteroid excretion rose from 5.4 to 27 mg. Proctoscopic examination four weeks after treatment was begun revealed

definite improvement of the mucosa. The granularity was distinctly finer, and there was no bleeding. Friability was present but to a less extent than previously. The polypoid excrescence seen on two previous occasions was no longer observed.

Follow-Up Studies.—The patient continued to improve after treatment was stopped. Two months following cessation of therapy the patient had gained 25 pounds, had an excellent appetite and was on an essentially full diet. There was no nocturnal diarrhea, tenesmus or abdominal distress, and the patient was passing three to four formed stools daily, free of occult blood. Proctoscopic examination revealed an essentially normal mucosa except for fine granularity and mild thickening of the mucosa. Fecal lysozyme was 4 units per gram, and the serum albumin was 4.7 Gm. and serum globulin 3.2 Gm. per 100 cc.

The patient returned to work one month later (February 1950), was on a full, unlimited diet and was passing one to three formed stools daily which gave negative reactions for occult blood. Roentgenograms revealed definite improvement of the colon, as evidenced by an increased caliber of the bowel, increased haustral markings and considerably less spasm. Proctoscopy disclosed no bleeding, friability or ulceration, but a fine granularity was still perceptible.

The improvement has continued, so that 16 months after treatment (January 1951) the patient has gained 40 pounds, has one to two formed evacuations daily, free of occult blood, and is on a full diet. Proctoscopy reveals an essentially normal mucosa except for fine granularity.

PATIENT B. F.—This 41 year old housewife had been a semi-invalid since 1943 because of ulcerative colitis which developed after her father's death and her husband's induction into the Army. She had been hospitalized five times for acute exacerbations of diarrhea, anemia and weight loss, which responded to dietary, antibiotic, detergent and supportive therapy after prolonged periods of hospitalization. Four months before admission a large draining fistula developed in the left perianal area, and since then she had fever, chills, weakness, cramping abdominal pain, anorexia, a 16 pound (7.3 Kg.) weight loss and six to 12 bloody mucoid diarrheal bowel movements daily. In the two days preceding admission, she had repeated episodes of persistent vomiting.

The patient was admitted to the hospital on March 17, 1950. The temperature was 101.6 F. on physical examination and the pulse rate 106. There was diffuse abdominal tenderness with voluntary muscle spasm and a tender granulating fistula above the anus in the left buttock, approximately 10 mm. in diameter.

Pertinent Laboratory Findings.—The hematocrit was 43 per cent. The corrected erythrocyte sedimentation rate was 26 mm. per hour, the leukocyte count 12,100 and the initial eosinophil count 96 per cubic millimeter. Blood chemical values were within normal limits, save for 30 minute sulfobromophthalein (bromsulphalein®) sodium retention of 19 per cent. Stool cultures grew Escherichia coli, Aerobacter aerogenes, Proteus vulgaris, beta hemolytic streptococci and enterococci. Stool guaiac reactions were 2 to 4 + and the stools were watery, containing excess mucus and gross blood.

A barium sulfate enema revealed diffuse narrowing, serration and loss of haustration, with multiple small ulcerations in the distal half of the transverse colon and the entire descending colon and rectum. The bowel proximal to the middle of the transverse colon was dilated and atonic. Motility of the small intestine and colon was increased.

The proctoscopic examination revealed a reddened, friable, thickened, freely bleeding mucosa covered with a glistening mucoid exudate over multiple small chronic ulcerations.

The patient was maintained for a control period of 10 days on a bland diet with no other therapy. She continued to have eight to 12 explosive bowel movements daily containing gross blood and an elevation in temperature to 102 F. daily. On the eleventh hospital day treatment with 25 mg. of ACTH every six hours intramuscularly was instituted.

The temperature fell precipitously to normal and remained normal, the chills disappeared and the patient felt considerably improved and experienced a sense of well-being and a remarkable increase in appetite within a few days. The stools diminished to five and six daily on the fourth day of treatment and became semiformed; the free drainage from the fistula diminished considerably. Two weeks after therapy was instituted, the nocturnal diarrhea disappeared and stools became formed and were free of gross blood.

Sigmoidoscopy 17 days after the onset of ACTH therapy revealed definite improvement, as evidenced by a decrease in the friability of the mucosa, a significant diminution in bleeding

and a rapid decrease in the size of the fistula to 6 mm. in diameter. Both the tenderness and the amount of drainage diminished dramatically.

The fecal lysozyme titer, which varied from 65 to 110 units before ACTH therapy was instituted, fell precipitously to 10 units per gram within three days of treatment and remained in the range of 6 to 10 units for the duration of hospitalization (fig. 2). The sedimentation rate fell from 32 mm. per hour to 10 mm. within a week of treatment and was 3 mm. two weeks later. The hematocrit, which had fallen to 36.5 per cent before ACTH treatment was begun, rose to 42 per cent within 12 days of treatment. There was an excellent eosinophil and ketosteroid response, as evidenced by a fall in the eosinophils from 96 per cubic millimeter before treatment to 0 within 48 hours and a rise in the urinary 17-ketosteroid excretion from 8.5 to 27.6 mg. per 24 hours.

The patient continued to do well throughout the remainder of the hospitalization, passing two or three formed stools daily, free of gross blood but containing a trace of occult blood. The lysozyme titer remained depressed, and the patient gained approximately 5 pounds (2.3 Kg.) during the three weeks of treatment. ACTH therapy (100 mg. daily) was continued for 21 days, from March 27 to April 16, 1950. Within one week the patient's face appeared rounded and moonlike, and two weeks later an acneform rash on the chest and back, as well as pigmentation of the elbows, hands and nipple areolas, was observed. This was accompanied with an increase in hair on the face.

Proctoscopic examination on April 24 showed continued improvement, with a mild residual friability and bleeding of the mucosa. The fistula was approximately 6 mm. in diameter.

The ACTH dosage was tapered off from 100 mg. a day on April 14 to 50 mg. daily on April 15 and 16. With the discontinuation of the therapy on April 17, the patient exhibited an elevation in temperature to 101 F. which was remitting in type. This fever continued from April 17 to May 4, with the temperature reaching a peak of 101 or 102 F. daily. There was no exacerbation of diarrhea, abdominal distress or loss of appetite, and the patient appeared to be progressing satisfactorily. There was a spontaneous remission in the fever on May 4, and the temperature remained normal thereafter.

Proctoscopic examination on May 8, 43 days after ACTH therapy was begun, revealed considerable improvement in the appearance of the mucosa. The granularity was barely perceptible, and the bleeding on trauma was negligible. The fistula had diminished at this point to 2 mm. in diameter, with no tenderness and little drainage. On May 15 the fistula was barely perceptible, measuring 1 mm. in diameter, and the proctoscopic appearance of the mucosa revealed continued improvement.

Roentgenologic examination disclosed an increased caliber of the colon, diminished spasm and motility and an increase of haustration, suggesting a definite improvement.

On discharge, May 18, the patient had gained 10 pounds in weight and was passing three formed stools daily which contained a trace of occult blood.

Follow-Up Observations.—The patient remained essentially well except for occasional episodes of diarrhea lasting one to two days following dietary indiscretion. She continued to have two or three formed bowel movements daily without gross blood and was maintained on a bland diet with cooked fruits and vegetables and no medicaments other than vitamins. The acne, hirsutism and pigmentation gradually disappeared over a period of six months. Repeated proctoscopic examinations during this period revealed healed mucosa with little evidence of activity. The mucosa, however, never returned to normal; there were persistent fine granularity and occasional slight bleeding on cotton swabbing. The patient remained clinically well; the fistula drained intermittently but remained pinpoint in size and was barely perceptible. Her appetite remained good, and there was no evidence of abdominal distress.

By October 15 the pigmentation, roundness of the face and hirsutism had completely disappeared. There was a weight gain of 21 pounds (9.5 Kg.). On November 20 the patient was having one or two formed bowel movements daily without gross blood; the fistula drained intermittently but very slightly. The patient's clinical condition was excellent, and she had gained a total of 24 pounds (10.9 Kg.) since her admission to the hospital.

On Dec. 25, 1950, approximately nine months after ACTH therapy was started, the patient had a mild relapse consisting of diarrhea with six to eight stools daily, containing rare flecks of gross blood, fever, anorexia and weight loss. These symptoms responded to a 10 day course

of oral treatment with cortisone (250 mg. daily), during which time a definite remission was produced. This attack was considerably milder than the previous one, did not require hospitalization and was brought under complete control within two weeks. Proctoscopic examination Jan. 23, 1951 revealed an essentially normal mucosa except for some thickening, and the patient was passing two formed evacuations daily without gross blood and had maintained her weight.

PATIENT E. G.—This 17 year old school boy, who was a long distance runner, was admitted to the hospital on June 25, 1950 because of diarrhea, consisting of 10 to 12 watery, blood-tinged or grossly bloody stools per day of four months' duration. Diarrhea and blood loss were aggravated by strenuous exercise and stress associated with his racing activities and were accompanied with abdominal distress, tenesmus and a 10 pound weight loss. Previous medical management did not appear to alter the severity of the diarrhea or the abdominal distress.

Physical examination disclosed no abnormalities except for evidence of weight loss and dehydration. The hematocrit was 43 per cent, serum albumin 3.9 Gm. and globulin 2.1 Gm. per 100 cc., corrected sedimentation rate 21 mm. per hour, eosinophil 756 per cubic millimeter and urinary 17-ketosteroid excretion 9.1 mg. per 24 hours. The stools contained gross blood and revealed no enteric pathogens on culture.

Proctoscopy showed a markedly friable, ulcerated, coarsely granular rectal mucosa with pinpoint bleeding throughout. The patient was placed on a regular hospital diet for seven days, during which time the diarrhea and gross blood persisted.

Administration of ACTH, 20 mg. every six hours, was begun on his seventh hospital day, and the patient was treated for 18 days, with a gradual diminution in the dose for the next three days. Within 24 hours his stool frequency diminished to two daily. Grossly visible blood disappeared on the sixth day of treatment, and the stools became formed for the first time in three months. On the thirteenth day of therapy his stools became guaiac negative. ACTH was the only medicament administered. It induced the usual eosinopenia (19 eosinophils per cubic millimeter) within three days and a urinary 17-ketosteroid increase to 20.9 mg. per 24 hours within seven days. The sedimentation rate fell to 12 mm. in one week, and the fecal lysozyme decreased to 4 units per gram within two days of ACTH therapy.

The patient experienced pronounced euphoria and a ravenous appetite and gained 5 pounds in two weeks. He was discharged on July 22 with 1 or 2 formed evacuations daily, free of occult blood. On the day of discharge the rectal and sigmoid mucosa was indistinguishable from normal.

After discharge, the patient did well except for occasional slight rectal bleeding after extensive exertion. His appetite remained good, and he continued to gain weight. In the middle of September 1950 the patient began training again for long distance, cross country track. Three days later he noticed the onset of severe diarrhea and bleeding with six or seven watery bowel movements daily containing gross blood, associated with severe anorexia, fatigue and lower abdominal pain. On October 3 he noticed an elevation in temperature to 102 F. and was readmitted to the hospital on October 4.

On admission the patient weighed 94 pounds (42.6 Kg.), appeared acutely ill and had an elevation in temperature varying from 100 to 102 F. Physical examination revealed abdominal tenderness in both the right and the left lower quadrant. On proctoscopic examination diffusely granular, ulcerated, freely bleeding, very friable mucous membrane was observed. Free blood gushed from the mucosa and obscured the field at frequent intervals. Hematocrit was 34 per cent and the sedimentation rate 33 mm. per hour. The white blood cell count was 18,600.

Two hundred milligrams of cortisone was administered daily in divided doses for 14 days (October 4 to 18), and then the dose was gradually tapered off to 25 mg. daily during the subsequent six days. During this period the patient continued to have a temperature elevation to 100 F. daily, his anorexia and diarrhea persisted and he continued to lose weight, so that on October 17 his weight had decreased to 90 pounds (40.8 Kg.) and the hematocrit continued to fall to 29 per cent in spite of an adequate eosinophil response.

ACTH therapy was begun on October 18, the patient receiving 80 mg. daily in four divided doses for four days and 120 mg. a day for 10 days. Then the dosage was tapered off to 40 mg. daily.

The characteristic sense of well-being, increased appetite, decrease in the number of stools and prompt fall in temperature did not occur until the dose was increased to 120 mg. a day,

after which a prompt remission occurred. After five days of the increased dose of ACTH, the patient felt exceedingly well, remained afebrile and had three formed and semiformed evacuations daily, all containing occult blood.

The patient continued to show improvement with ACTH administration, regained the weight he had lost during the first part of his hospitalization and was discharged on November 5 weighing 95 pounds (43.1 Kg.). The hematocrit on discharge was 34 per cent, and the stool reactions were consistently positive for occult blood.

Proctoscopic examination on November 6 revealed considerable improvement in the appearance of the mucosa. The lower 4 inches (10 cm.) of the rectal mucosa appeared almost normal. There was some fine granularity but no bleeding or friability. At the junction of the rectum and sigmoid, on the right lateral wall, the mucosa was hyperemic and very friable and bled profusely on trauma. This was localized to an area approximately 1 inch (2.5 cm.) in diameter. It was felt that the patient's improvement in general, however, had been excellent in view of the fulminating course of the disease.

The patient continued to improve while receiving 40 mg. of ACTH daily in divided doses. He had three or four semiformed evacuations daily without gross blood, and his hematocrit rose to 38 per cent.

ACTH treatment was stopped on November 21. The patient continued to do well until December 5, at which time he began to have severe diarrhea, five or six watery bowel movements a day with profuse gross blood. In spite of three transfusions and chloramphenicol (chloromycetin®) therapy, the course continued to go downhill and the hematocrit on December 19 was 29 per cent. He suffered from almost complete anorexia, and his weight on December 26 had fallen to 85 pounds (38.6 Kg.).

He refused hospitalization, and on December 26 oral administration of cortisone, 125 mg. every 12 hours, was begun. On Jan. 2, 1951 he noted a definite increase in appetite and a decrease in diarrhea and blood loss. The patient continued to improve, and on January 16 the dose of cortisone was decreased to 150 mg. daily. His appetite improved tremendously, and he gained 12 pounds (5.4 Kg.) from December 26 to January 16. He was passing two or three formed or semiformed stools daily without gross blood, had no abdominal distress whatever and appeared to be progressing satisfactorily.

Dr. George W. Thorn, Dr. Peter Forsham and Dr. Thomas A. Warthin cooperated in these studies. Dr. John R. Mote, of The Armour Laboratories, Chicago 9, supplied us with the ACTH used in these studies.

A MORTALITY STUDY IN BUNDLE BRANCH BLOCK

MANUEL RODSTEIN, M.D.
RICHARD GUBNER, M.D.
JOHN P. MILLS, B.S.
JOSEPH F. LOVELL
AND
HARRY E. UNGERLEIDER, M.D.
NEW YORK

BUNDLE branch block has long been regarded as an ominous electrocardiographic sign. Numerous instances have been reported of prolonged survival of subjects with bundle branch block, and several studies have indicated that survival in the presence of this abnormality is considerably longer than was originally believed.

These studies, however, have varied widely in the number of subjects followed, the time interval over which they were followed and the statistical methods employed in calculating the results obtained.[1] They have in common the fact that they were derived from patient records from hospitals, outpatient departments and private practices.

In view of the fact that no mortality study has as yet been published on a group of persons not under medical care at the time of discovery of the lesion, it was felt worth while to review the accumulated electrocardiographic records of the Equitable Life Assurance Society of the United States for the presence of cases of bundle branch block and to conduct a mortality study of these persons.

From the Medical Department, Equitable Life Assurance Society of the United States.

1. (*a*) Wood, F. J.; Jeffers, W. A., and Wolferth, C. L.: Follow-Up Study of 64 Patients with a Right Bundle Branch Block Defect, Am. Heart J. **10**:1056, 1935. (*b*) Sampson, J. J., and Nagle, O. E.: The Prognosis of Bundle Branch Block and Other Intraventricular Conduction System Defects, Am. J. M. Sc. **191**:88, 1936. (*c*) Graybiel, A., and Sprague, H. B.: Bundle Branch Block: An Analysis of 395 Cases, ibid. **185**:395, 1933. (*d*) Freund, H. A., and Sokolov, R.: Bundle Branch Block, Arch. Int. Med. **63**:318 (Feb.) 1939. (*e*) Bayley, R. H.: The Frequency and Significance of Right Bundle Branch Block, Am. J. M. Sc. **188**:236, 1934. (*f*) Willius, F. A.; Dry, T. J., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram: I. General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs and Wide S Wave Pattern, Based on 1,611 Cases, Arch. Int. Med. **67**:1008 (May) 1941. (*g*) Reeser, R., Jr.; Willius, F. A., and Dry, T. J.: Life Expectancy in Conductive Disturbances Affecting Ventricular Complex of Electrocardiogram: II. Special Consideration of Bundle Branch Block with Concordant Graphs and with Discordant Graphs, ibid. **67**:1027 (May) 1941. (*h*) Dry, T. J.; Willius, F. A., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting Ventricular Complex of Electrocardiogram: III. Special Consideration of the Wide S Wave Pattern, with Report of 3 Cases, ibid. **67**:1034 (May) 1941. (*i*) Kaplan, L. G., and Katz, L. N.: The Prognosis of Intraventricular Block, Am. Heart J. **18**:145, 1939.

PRESENT STUDY

The files of the Diagnostic Laboratory of the Society include approximately 30,000 cases with electrocardiograms, accumulated since 1929. These electrocardiograms were obtained from among a much greater number of applicants for insurance for the following reasons: application for a large amount of insurance; a history of having had an electrocardiogram made in the past for whatever reason; a history of or the presence of symptoms suggestive of cardiac disease; the history of or the presence of cardiac abnormalities, such as tachycardia, bradycardia, premature contractions, abnormal rhythms, cardiac murmurs, abnormal blood pressure or cardiac enlargement; the history of or the presence of glycosuria.

Virtually all persons with obvious cardiovascular disease who were evidently uninsurable at the time of original examination were excluded from further study at the Diagnostic Laboratory, so that the majority of subjects with whom the present investigation is concerned exhibited either no physical impairments or impairments of such minor degree as would not preclude their insurability.

Only records in which there was a QRS interval of at least 0.12 second in width in the standard leads were included, unless enough precordial leads were available to make a diagnosis of bundle branch block by the latter means. Inasmuch as the records dated back to 1929 in some cases, the majority had only one precordial lead. Therefore, a certain error was inevitable in the classification of the type of block. The incidence of right bundle branch block was also probably somewhat lowered, as Wilson [2] has shown that right bundle branch block may occur with a QRS interval of 0.10 second in width in the standard limb leads.

In all, 193 cases of bundle branch block were discovered, an incidence of less than 1 per cent. The type of bundle branch block was classified as right in 131, left in 52 and atypical in five, while in five cases the defect was of the Wolff-Parkinson-White type. These persons were followed from the time of their medical examination for insurance to their death, or to July 1, 1949 if they survived. There were only four persons who could not be traced. The 10 subjects with atypical and Wolff-Parkinson-White types of block were excluded from the mortality study because of the small size of these groups. The remaining 183 subjects with right and left bundle branch block were divided into the following four groups:

Group A consisted of 36 persons who would have been considered as standard risks for insurance if they had not shown bundle branch block in their electrocardiograms; 31 had right and five left bundle branch block. In this group there were no findings on history, physical examination, roentgenogram or electrocardiogram, other than bundle branch block, on which a diagnosis of cardiovascular or other disease could be made.

Group B consisted of 35 persons who would have been considered as substandard risks for insurance, except for the presence of bundle branch block; 26 had right and nine left bundle branch block. The factors which caused the classification of this group as substandard were primarily minor cardiac defects. These were for the most part systolic apical murmurs of varying degrees of constancy, intensity and transmission, borderline blood pressure readings and minor electrocardiographic abnormalities, such as premature contractions and prolonged P-R intervals.

Group C consisted of 29 persons for whom sufficient data were not available for complete insurance classification; 20 had right and nine left bundle branch block. However, enough data were available so that it could be seen that the nature of the cardiac and other defects present was minor and corresponded to that of the defects present in group B.

Group D consisted of 83 persons who would have been declined for insurance irrespective of the finding of bundle branch block; 54 had right and 29 left bundle branch block. The great majority would have been declined for reasons of major cardiac abnormalities, such as hypertension and cardiac enlargement.

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2. Wilson, F. N.: Concerning the Form of the QRS Deflection of the Electrocardiogram in Bundle Branch Block, J. Mt. Sinai Hosp. **8**:1110, 1942.

Each of the four groups was further divided into two subgroups, those with right and those with left bundle branch block, and the expected deaths were computed for each of the eight subgroups by means of the Equitable Life Assurance Society 1940-1945 Standard Ultimate Mortality Table.[3]

RESULTS

The results are given in table 1. The groups A, B and C described above showed only insignificant differences in mortality ratios and have been combined to give a more stable result; they can be considered as representing a probably insurable group with no or only minor impairments. In order to obtain the upper limit for the mortality ratios, it was assumed that the four applicants who could not be traced died immediately after the examination. The resulting number of deaths and mortality ratios are shown in parentheses in the table.

TABLE 1.—*Mortality of Insurance Applicants with Bundle Branch Block*

Underwriting Classification When Bundle Branch Block Was Disregarded	Left Bundle Branch Block			Right Bundle Branch Block			Totals		
	No. Cases	Actual Deaths	Mortality Ratio (Actual to Expected Deaths), %	No. Cases	Actual Deaths	Mortality Ratio (Actual to Expected Deaths), %	No. Cases	Actual Deaths	Mortality Ratio (Actual to Expected Deaths), %
Insurable (standard or substandard), groups A, B, C	23	6	146 ± 40	77	12 (13)	111 ± 21 (121 ± 22)	100	18 (19)	121 ± 19 (128 ± 20)
Uninsurable, group D	29	11 (12)	261 ± 58 (309 ± 57)	54	15 (16)	186 ± 32 (199 ± 33)	83	26 (29)	212 ± 19 (236 ± 29)

The figures in parentheses are based on the assumption that "lost" cases became deaths immediately after examination.

TABLE 2.—*Comparison of Mortality Ratios*

Underwriting Classification When Bundle Branch Block Was Disregarded	Actual Deaths	Mortality Ratio (Actual to Expected Deaths), %
Standard risks (no cardiac or other defects)	8	126 ± 29
Substandard risks or declined for cardiac reasons only	21	194 ± 28

The probable error of the mortality ratios, where the groups were large enough to compute them, are shown in plus or minus per cent in the table.[4]

In considering table 1, it should be remembered that a substantial portion of the exposure in this series occurred in the thirties, when mortality rates were higher than in 1940 to 1945, which is the base period for rates used in calculating the expected deaths in this series.

3. In effect, this uses persons insured by the Society as a control group. This control group consisted of persons who had been insured by the Society at standard rates for at least 15 years prior to their entry into the period of observation, 1940 to 1945, so that any effects of the initial medical examination in lowering mortality during the early policy years are no longer present and the rate of mortality becomes a function of the person's attained age. The mortality of the control group is taken as 100 per cent; therefore, the ratio of actual to expected deaths of, say, 129 per cent of a subgroup in the table indicates that the mortality of those in the group in question is 29 per cent greater than that in the control group with the same age distribution.

4. The significance of probable error figures can be explained by the following example. The mortality of the entire probably acceptable group (A, B, C) is 121 per cent (probable error ± 19 per cent) and means that there is only one chance in 20 that the sample here investigated came from a universe whose true mortality was outside the limits (121 per cent — 3 [19 per cent]) and (121 per cent + 3 [19 per cent]), or 63 and 178 per cent.

In table 2 the mortality ratios of the group who showed no cardiac or other defect except for the presence of bundle branch block and who would have been considered as standard risks for insurance are compared with the mortality ratios of those subjects with only cardiac defects of any kind in addition to the presence of bundle branch block.

COMMENT

The true incidence of bundle branch block in the population as a whole is unknown. It has been estimated that in healthy young adults without heart disease it is rare, and figures of less than 1 per cent have been mentioned.[5] Among 1,300 unselected students Wood[1a] found only two cases, both of right bundle branch block. It is also obvious that there is an increase in incidence with age, as is shown by the same author's[1a] finding of five cases, all of right bundle branch block, among 145 unselected executives and by the report of an incidence of 13 per cent in a population of 300 inmates over 60 years of age[6] in an old people's home. The incidence of less than 1 per cent in this series is lower than that of most reported series, i. e., 3.5 per cent,[1b] 2.5 per cent[1c] and 1.5 per cent.[7] This increased incidence is a reflection of the hospital type of patient studied and of an older age group, with the exception of Langley's[7] series, which was drawn from the patients admitted to a United States Naval Hospital on whom electrocardiograms were taken during World War II. The true incidence in the general population is undoubtedly less than 1 per cent, as is obvious from a perusal of the reasons for which tracings were obtained in this series.

In previously reported series left bundle branch block has been predominant in incidence,[8] and only in one[7] have the numbers been approximately even. In this series the incidence of right bundle branch block is greatly in excess of that of left, 131 to 52 cases. The greater incidence of right bundle branch block is particularly evident in the younger age group. Thus, of 30 persons below the age of 40 in this series, there were only three (10 per cent) with left bundle branch block, as compared with 27 (90 per cent) having right bundle branch block. The relative frequency of left bundle branch block increased with advancing age. In the group 40 to 49 years of age, 24 per cent of a total of 49 persons, in the age group of 50 to 59 years 28 per cent of a total of 65 persons and in the group 60 to 69 years old, 49 per cent of 39 persons had left bundle branch block.

In this series more than 50 per cent of the subjects had little or no demonstrable cardiac involvement. That this is frequently the case has been shown by various authors. Langley[7] reported 29 of his 100 naval personnel with bundle branch block to have completely negative findings. Wood[1a] noted among 64 persons with right

5. Nichols, E.: Transient Right Bundle Branch Block, Wide S Wave Type, in Which Normal Conduction Occurred Both Spontaneously and in Response to Vagal Stimulation, Ann. Int. Med. **30**:196, 1949.

6. Fox, T. T.; Klements, J., and Mandel, E. E.: Electrocardiographic Changes in Old Age, Ann. Int. Med. **17**:236, 1942.

7. Langley, R. W.; Reed, J. C., and Utz, D. C.: Bundle Branch Block: A Review of 100 Cases, Am. Heart J. **33**:730, 1947.

8. Footnote 1 *d* and *e*. Master, A. M.; Kalter, H.; Dack, S., and Jaffee, H. S.: The Relation Between Bundle Branch Block and Cardiac Enlargement, Am. Heart J. **20**:186, 1940. White, P. D.: Heart Disease, New York, The Macmillan Company, 1944, p. 939.

bundle branch block 20 with no and 15 with only minor cardiac changes. Fisch[9] has reported on 11 persons with right bundle branch block with essentially normal findings. In this series subjects with no cardiac involvement were found among those with left as well as those with right bundle branch block. It is probable that in an unselected general population the percentage of such persons would be even higher.

Congenital heart disease, rheumatic heart disease, cardiac enlargement and hypertension were much higher in frequency in previously reported series with bundle branch block than in the present series.

The causes of death in this series correspond remarkably well with those of the population as a whole of a similar age group. Twenty-two of a total of 46 deaths, or 48 per cent, were of a cardiac nature. The figure for white men between the ages of 45 and 64 in 1947 for the United States was 41 per cent.[10] In the group which would have been uninsurable, even though bundle branch block had not been present, death due to cardiac disease were 54 per cent of the total and in the insurable group 44.5 per cent. There was no remarkable difference in the causes of death in the group with left as compared to that with right bundle branch block.

A study of the mortality figures presented in the tables brings out the fact that the mortality of the probably insurable group, disregarding the presence of bundle branch block, is remarkably good. The figure of 121 per cent, with a probable error of ± 19 per cent, is even better when, as previously mentioned, the factor of a considerable portion of the exposure having occurred in the thirties is noted. The mortality rates were higher in this period than in the period 1940 to 1945, which is the base period used for calculating the expected deaths.

While it was anticipated that the mortality of the subjects with left bundle branch block would exceed that of those with right bundle branch block, the differences in mortality, as shown in table 1, were not very considerable.

There were no deaths in the first two years in the group considered insurable had bundle branch block not been present. Long survivals were common in both groups. Of the 78 persons first examined in 1939 or earlier, 46 were still alive on July 1, 1949. The average exposure of the entire group was eight years. The average age at the time of initial medical examination of the groups presented in table 1 did not show any remarkable variation, except for a somewhat higher age in the subjects with left bundle branch block. The 23 persons with left bundle branch block who had no other major impairments averaged 55 years of age; the remaining 29 with left bundle branch block averaged 54 years; the 77 persons with right bundle branch block without other major impairments averaged 46.8 years of age, and the remaining 54 with right bundle branch block averaged 50 years.

The over-all average age at the time of initial medical examination of the probably insurable group of 100 persons (disregarding the presence of bundle branch block) was 48.7 years and of the 83 uninsurable persons 51.4 years.

9. Fisch, C.: Bundle Branch Block of the Broad S Type: Report of 11 Cases Without Any Evidence of Heart Disease with One Instance Showing Partial and Transient Block, J. Indiana M. A. **40**:1128, 1947.

10. Manpower for National Defense, Statistical Bulletin, New York, Metropolitan Life Insurance Company, 1950, vol. 31, no. 8.

In table 2 an attempt is made to show the effect on mortality of the presence of cardiac impairments of any degree in addition to bundle branch block as contrasted to the group whose only demonstrable impairment was bundle branch block. There is an increase in mortality of possible statistical significance in the group with the cardiac impairments as compared with the group having bundle branch block alone.

Because of the difference in methods in studying the effects on mortality of the presence of bundle branch block, this study cannot be compared in detail with other studies previously cited in this article. However, the impression obtained is that the results are more optimistic and that the presence of bundle branch block alone in the absence of major cardiac abnormalities does not imply an excessively high mortality.

CONCLUSIONS

Bundle branch block is an infrequent lesion in the general population.

Right bundle branch block is of much greater frequency than left bundle branch block, particularly in younger age groups.

Bundle branch block is commonly associated with little or no demonstrable cardiovascular impairment.

The presence of bundle branch block per se does not imply a high mortality in the absence of other major cardiac abnormalities.

The difference between the mortality in right and that in left bundle branch block is relatively slight.

RELAPSING PANNICULITIS (WEBER-CHRISTIAN DISEASE)

Review of Literature and Report of a Case Including Treatment with Cortisone

CHARLES R. SHUMAN, M.D.
PHILADELPHIA

A CASE OF relapsing panniculitis (Weber-Christian) disease has been extensively studied for approximately 21 months, from the inception of the disease until the death of the patient. In this paper is outlined the course of the illness with the various studies conducted in an effort to ascertain the cause and the possible lines of therapy which may aid in the management of patients with this disease. The disease occurs in various grades of severity, from that of a relatively benign course to the overwhelming picture of toxicity manifested in the present case.

The illness is termed relapsing, febrile, nodular, nonsuppurative panniculitis. The second word of this title was added by Christian [1] in 1928 to the original descriptive designation by Weber,[2] who accurately reported the disease in 1925. Previously, Pfeiffer [3] in 1892 and Gilchrist and Ketron [4] in 1916 had described the clinical and histopathological features of this disease. During recent years numerous reports have appeared, and cases now total 54, of which seven were studied at autopsy. A similar disease occurring in rabbits has been described by Duran-Reynals.[5]

The characteristic feature of Weber-Christian disease is the occurrence of nodular masses of fat in the subcutaneous tissue. These areas of panniculitis vary from 1 cm. in diameter to large masses, one of which in the present case was 28 by 8 cm. These lesions are often painless but may be somewhat tender. They are firm and movable and may be adherent to the skin, which becomes reddened and violaceous, with roughening and scaling. Their development is gradual, and they may be unnoticed unless searched for. As the lesion ages, it tends to show central clearing and softening so that a saucer-like appearance or dimpling is observed. The nodules may then disappear within several days or months, or they may persist. The skin remains discolored over the area, or occasionally there is

Dr. Shuman is Instructor in Medicine, Temple University Hospital.

1. Christian, H. A.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Arch. Int. Med. **42**:338-351 (Sept.) 1928.

2. Weber, F. P.: Relapsing Non-Suppurative Nodular Panniculitis Showing Phagocytoses of Subcutaneous Fat Cells by Macrophages, Brit. J. Dermat. **37**:301-311, 1925.

3. Pfeiffer, V.: Über einen Fall von herdweiser Atrophie des subcutanen Fettgewebes, Deutsches Arch. klin. Med. **50**:438-449, 1892.

4. Gilchrist, T. C., and Ketron, L. W.: A Unique Case of Atrophy of the Fatty Layers of the Skin, Preceded by the Ingestion of Fat by Large Phagocytic Cells; Macrophages, Johns Hopkins Hosp. Bull. **26**:291-294, 1916.

5. Duran-Reynals, F.: A Necrotizing Disease in Rabbits Affecting Fatty and Muscular Tissues: Analogies with Weber-Christian Disease of Humans, Yale J. Biol. & Med. **18**:583, 1946.

no trace of the previous lesion. These nodular masses are widely distributed, occurring most commonly on the abdomen, breasts, thighs, pectoral regions and arms, but they may be found in other areas. They do not become suppurative and are sterile on culture, although they may undergo necrosis and liquefaction.

The appearance of the lesion is associated with fever of a septic type, with daily temperature rises to as high as 105 F., during which the patient complains of weakness, malaise, muscle pains and anorexia. Occasionally nausea and vomiting are present. Constitutional symptoms may be severe or may be relatively minor over a period of many years. In the present case two remissions of short duration occurred during treatment. Christian [1] noted a remission of three years' duration in his case. One patient was free of the disease 27 years after the initial diagnosis,[4] when mentioned in the discussion on the paper by Miller and Kritzler.[6]

Epidemiological features of the disease disclose no seasonal or climatic factors of importance in its incidence. It is not infectious and has never been transmitted from a patient to another person or animal. The disease preponderates in the female and has been observed in persons of every age group from 6 months to 70 years, although its peak incidence occurs in the group 20 to 40 years of age. Many persons with this disease are overweight at its onset.

Laboratory tests reveal no specific changes which characterize the disease. Results of blood chemical studies, including determinations of lipase, lipid fractions, protein, dextrose tolerance, chlorides, bromides, iodine and many others, have not been abnormal. Liver function has varied somewhat,[7] but in the present case it was normal, as it has been in numerous other reported cases. The hematological picture also varies. In the present case serious anemia and leukopenia persisted throughout the disease. Such findings have been previously noted.[8] However, the hemoglobin content may be normal,[9] and the leukocyte count may be normal [10] or

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6. Miller, J. L., and Kritzler, R. A.: Nodular, Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **47**:82-96 (Jan.) 1943.

7. (*a*) Miller and Kritzler.[6] (*b*) Mostofi, E. K., and Engleman, E.: Fatal Relapsing Febrile Nonsuppurative Panniculitis, Arch. Path. **43**:417-426 (April) 1947. (*c*) Spain, D. M., and Foley, J. M.: Nonsuppurative Nodular Panniculitis (Weber-Christian's Disease), Am. J. Path. **20**:783-787, 1944.

8. (*a*) Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **109**:1419-1425 (Oct. 30) 1937. (*b*) Bunnell, I. L., and Levy, D. S.: Weber-Christian's Disease: Report of Case, Ann. Int. Med. **28**:169-172, 1948. (*c*) Friedman, N. B.: Fatal Panniculitis and Autopsy, Arch. Path. **39**:42-46 (Jan.) 1945. (*d*) Johnson, W. A., and Plice, S. G.: Relapsing Febrile Nodular Nonsuppurative Panniculitis: A Report of a Case with a Review of the Literature, ibid. **48**:281 (Oct.) 1949. (*e*) Rosenberg, W. A., and Cohen, T. M.: Relapsing Febrile Nonsuppurative Panniculitis (Weber-Christian Disease), Illinois M. J. **81**:59-62, 1942.

9. (*a*) Arnold, H. L., Jr.: Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Preliminary Report of a Case Controlled by Sulfapyridine, Arch. Dermat. & Syph. **51**:94-99 (Feb.) 1945. (*b*) Binkley, J. S.: Relapsing Febrile Nodular Nonsuppurative Panniculitis: Report of a Case, J. A. M. A. **113**:113-116 (July 8) 1939. (*c*) Larson, C. P., and Ootkin, B. N.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Report of Case, Am. J. Clin. Path. **11**:781-787, 1941. (*d*) Niedermayer, A. J., and Moran, T. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis: Report of Case Treated with Penicillin, Ann. Int. Med. **29**:958-964, 1948. (*e*) Pierini, L. E.; Irigoyen, L., and Ugazio, D. A.: Paniculitis nodular recidivante no suppurativa febrile (Weber-Christian), Publ. d. Centro de invest. tisiol. **10**:97-124, 1946. (*f*) Rubin, S. H., and Bland, J. H.: Relapsing Febrile Nonsuppurative Panniculitis, Am. J. Med. **7**:288, 1949.

elevated.[11] Differential counts are not disturbed. The bone marrow is not unusual and is reflected in the state of the peripheral blood count.

The clinical picture of Weber-Christian disease, with the characteristic nodules appearing in association with fever and constitutional symptoms, should lead to the diagnosis. Confirmation of the diagnosis is obtained by biopsy of the subcutaneous lesions. The pathological picture is that of an infiltration of the fat with large numbers of lymphocytes and monocytes and occasional polymorphonuclear leukocytes. The interstices of fat between individual fat cells are congested with these leukocytes so that they are separated and may undergo atrophy. Phagocytosis of fat cells is frequently present, producing foamy vacuolated macrophages. Fibrous scarring may replace an area of inflamed fat so that dimpling of the skin occurs. The process is limited to the panniculus, although infiltration of peritoneal, periadrenal, pericardial, omental and mesenteric fat [12] has been seen. Vascular alterations in the involved fat have been described.[13]

Seven autopsies have been reported in cases of this disease. One patient died of tuberculosis [13d] and one of chronic glomerulonephritis.[7c] Two patients died with intercurrent pyogenic infection, peritonitis [12b] and staphylococcic septicemia.[8c] One patient died of Hodgkin's disease.[14] Two others died of their disease, with widespread involvement of fat and necrosis and fatty infiltration of the liver.[15] In other fatal cases, as in the present one, autopsy was not performed.

REPORT OF CASE

C. P., a 30 year old white man, was employed as a forger in a steel plant. He was in good health until Dec. 2, 1948, at which time he was struck on the left foot with an iron bar. Pain in the left leg, with fever and easy fatigability, persisted about one week following the trauma. Several days later, he noted pain in the right lower abdominal quadrant and right groin for a three day period. This pain was somewhat relieved by manual pressure applied over the right groin. At this time, loose bowel movements developed and he continued to feel extremely weak.

10. (*a*) Arnold.[9a] (*b*) Binkley.[9b] (*c*) Netherton, E. W.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **28**:258-259 (Aug.) 1933. (*d*) Larkin, V. deP.; DeSanctis, A. G., and Margulis, A. E.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), Am. J. Dis. Child. **67**:120-125 (Feb.) 1944.

11. (*a*) Brill, I. C.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher, Baltimore, Waverly Press, Inc., 1936, pp. 694-704. (*b*) Brudno, J. C.: Chronic Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Relation to Rheumatic Fever and Allied Diseases, New England J. Med. **243**:513-517, 1950. (*c*) Reed, A. C., and Anderson, H. H.: Relapsing Nonsuppurative Panniculitis, California & West. Med. **47**:325-327, 1937.

12. (*a*) Spain and Foley.[7c] (*b*) Ungar, H.: Relapsing Febrile Nodular Inflammation of Adipose Tissue (Weber-Christian Syndrome): Report of a Case with Autopsy, J. Path. & Bact. **58**:175, 1946.

13. (*a*) Arnold.[9a] (*b*) Cummins, L. J., and Lever, W. F.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian's Disease): Report of 2 Cases, Arch. Dermat. & Syph. **38**:415-426 (Sept.) 1938. (*c*) Miller and Kritzler.[6] (*d*) Tilden, I. L.; Gotshalk, H. C., and Avakian, E. V.: Relapsing Febrile Nonsuppurative Panniculitis: Report of 2 Cases, Arch. Dermat. & Syph. **41**:681-689 (April) 1940. (*e*) Zee, M. L.: Nodular Nonsuppurative Panniculitis Treated with Penicillin, J. A. M. A. **130**:1219-1220 (April 27) 1946.

14. Hallahan, J. D., and Klein, T.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian's Disease): Review of Literature and Report of Case, to be published.

15. Miller and Kritzler.[6] Mostofi and Engleman.[7b]

However, the patient returned to work in January despite his symptoms, and on January 12 he was struck a severe blow in the right flank by a poker. A day or so following this injury the patient stated that a progressively enlarging mass appeared in the right flank. Prior to this accident he had experienced fever accompanied with profuse night sweats and had noticed impotence for several weeks. He was referred to another hospital, where he was found to have an elevation in temperature and a mass about 6 cm. in diameter in the right flank just above the iliac crest. The skin overlying the mass was red and thickened. This mass was removed and was found to consist of indurated fat. The induration extended to the underlying muscles, but there was no involvement of the muscular layers or further extension of the inflammatory process. Despite surgical treatment the symptoms remained present. The surgical incision did not heal but continued to drain a serous fluid. He was transferred to Temple University Hospital after negative results to a large number of studies had been obtained.

A review of the past medical history disclosed that the patient had had diphtheria at the age of 15 and difficulty with hearing since the age of 16 years after a blow to the ears in a fight. He has had recurrent grip every January and February for three years.

Systemic review did not disclose any further symptoms.

Physical examination revealed a robust, slightly obese, well nourished white man. There was partial bilateral conductive deafness. The blood pressure was 126/80. The pulse rate was 90, with normal sinus rhythm. The heart was not enlarged, and there were no murmurs. The abdomen was soft, and no masses were palpable. At the site of the previous operation in the right flank, an 8 cm. open incision drained a thin serous fluid. Two large nontender masses covered by thick, scaling, reddened skin were adjacent to the area.

The patient's temperature varied from 105 F. to normal, with wide diurnal fluctuations. His general condition remained good in spite of the persistent fever. However, he had progressive anemia and leukopenia despite some weight gain during the early weeks of his hospital course. Blood cultures obtained on six occasions yielded no pathogens. Numerous stool and urine cultures were also negative. Cultures obtained from the open incision showed a few Staphylococcus pyogenes var. aureus, coagulase-positive organisms. Spinal fluid culture was negative. Stools were repeatedly negative for ova and parasites. A number of biopsy specimens were obtained from the nodular, inflamed panniculus. Culture of this biopsy material was negative for pathogenic organisms. Direct examination and cultures for fungi also gave negative results in 15 preparations; Actinomycetes were constantly searched for. Blood studies for Streptococcus M.G. agglutination and cold agglutination and the Hirst test for Hemophilus influenzae gave negative results. The heterophil antibody reaction was negative. Smears revealed no malarial parasites. Agglutination studies for typhoid, paratyphoid, Pasteurella tularensis and Brucella organisms and the Weil-Felix reaction were all negative on two occasions. The skin reactions to tuberculin, histoplasmin, coccidioidin and blastomycin were negative.

Inasmuch as all microbiologic and serologic determinations were unrevealing and no offending organism could be found, the patient was given extensive trials with a variety of antibiotic agents. These included (1) penicillin, 100,000 units every two hours, for four weeks; (2) streptomycin, 250 mg. every four hours, for three weeks; (3) aureomycin, 250 mg. every three hours, for six weeks; (4) sulfadiazine for four weeks; (5) a full course of emetine hydrochloride given intramuscularly (0.065 Gm. daily for 12 days); (6) bacitracin administered locally to the area of the incision for two months, and (7) 0.3 Gm. of neoarsphenamine given intravenously.

None of these antimicrobial agents had any influence on the course of the disease. Biopsy material was sent to the Children's Hospital of Philadelphia to Dr. Michael Sigel. This material was injected intracerebrally and intranasally into mice and into chick embryos. These tests yielded negative results for the presence of vital agents.

The patient had numerous roentgenologic studies. The first of these was a chest roentgenogram which revealed some stringy density in the lower lobe of the left lung. This examination was repeated within a few weeks, and the lung was found to be essentially normal. A gastrointestinal series and studies with a barium sulfate enema were performed, both of which were normal. An intravenous urogram revealed no pathological changes. A roentgenogram of the skull was made on two occasions and showed no abnormalities. Electroencephalograms were obtained on three occasions with variable results. There was some evidence of diffuse impair-

ment of cerebral function. An electrocardiogram was normal. The patient's blood count ranged from 12 to 8 Gm. of hemoglobin with 4,520,000 to 2,500,000 erythrocytes. The white blood cell count at the time of admission was 4,100, with 58 per cent polymorphonuclear forms, 32 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. During the latter months of the first hospitalization the white blood cell count decreased to 2,500, with a normal differential count. However, there was always an increase in the nonfilamented forms. Bone marrow studies were obtained which demonstrated normoblastic hyperplasia, with an increase in the eosinophilic myelocytes and a decrease in the mature neutrophils and lymphocytes. Biopsy material was studied pathologically on several occasions. The diagnosis made by Dr. Ernest Aegerter on the biopsy material was chronic panniculitis of the Weber-Christian type.

While the patient was being studied in the hospital, 12 new lesions appeared at various sites over the abdomen, the lower extremities and the trunk. Two of these lesions disappeared after a two week interval. The remainder of the lesions progressively increased in size. They were subcutaneous in location, firm, nodular, circumscribed and nontender and were covered by skin which appeared violaceous and thickened. There was no increased warmth in the area of these fatty tumors.

On Aug. 8, 1949 a course of x-ray therapy was started. It was felt that this type of treatment might be of benefit because the chronic, nonspecific, inflammatory granulomatous reaction was thought perhaps susceptible to x-ray therapy. Dr. Robert Robbins advised 200 r twice a week, for a total of 400 to 600 r to each area. After this course of x-ray treatment, the patient's temperature returned to normal for the first time in nine months and remained normal until the end of September, a period of almost two months. The white cell count continued to drop, necessitating a number of transfusions. During this period of remission the patient felt extremely improved. X-ray therapy definitely altered the course of the illness. Dramatic recession in temperature elevation and considerable subjective improvement in the patient occurred. Prior to this treatment the patient had become despondent and was losing weight. After x-ray treatment he was alert and anxious to recover and gained 20 pounds (9.1 Kg.). His previous anorexia had disappeared; the headaches that he had experienced frequently during his illness became mild and infrequent. The libido, which had disappeared with the inception of his illness, definitely returned.

During October, three months later, as the patient's temperature rose to 103 and 104 F., it was obvious that the disease had again relapsed, and the patient was given another trial of x-ray therapy, this time without benefit. Similar failures of response of panniculitis to x-ray therapy have been reported.[16] It was hoped that nitrogen mustard (methyl-*bis* or *tris* [2-chloroethyl] amine hydrochloride) could be used in the treatment of the disease, but because of the persistent leukopenia it was felt unwise to administer this drug to a seriously ill patient. Tripelennamine (pyribenzamine®) hydrochloride, 400 mg. a day, was administered up to the time of discharge without significantly influencing the course of his disease.

Among the other laboratory determinations made on the first admission, serum proteins were found to be 6.6 Gm., with a normal albumin to globulin ratio, 4.4 Gm. of albumin to 2.2 Gm. of globulin. Repeated urinalyses revealed a normal condition, the specific gravity averaging 1.024. Two Robinson-Power-Kepler water tests were performed, and results of both were found to be positive in the first and second phases. Serum chlorides were 335 mg., and blood urea nitrogen was 13 mg. per 100 cc. Liver function studies, including cephalin flocculation, thymol turbidity and sulfobromophthalein (bromsulphalein®) sodium secretion, showed no abnormality. The patient was discharged on Dec. 12, 1949, with two new lesions appearing in the left breast and right axilla several days prior to discharge.

Second Admission (Feb. 25 to May 11, 1950).—The patient was asked to return to the hospital February 25 for a course of treatment with cortisone acetate. He stated that during the two month interval out of the hospital he had noticed the appearance of numerous new

16. (*a*) Alderson, H. E., and Way, S. C.: Relapsing Febrile Nonsuppurative Panniculitis (Weber), Arch. Dermat. & Syph. **27**:440-449 (March) 1933. (*b*) Fraser, J. F.: Nonsuppurating Panniculitis (Weber-Christian), ibid. **45**:810-811 (April) 1942. (*c*) Friedman.[8c] (*d*) Pierini and others.[9e]

areas of panniculitis. He had experienced a persistent elevation of temperature; he had remained weak and was unable to perform any work. Ankle edema appeared about one month after his discharge from the hospital. He had felt somewhat unsteady on his feet on walking and noticed an increasing sense of imbalance. Several weeks prior to his readmission he began to complain of stiffness of the hands and feet, with crampy pains affecting his extremities at night, suggesting tetany.

Examination at the time of readmission, February 25, disclosed a pallid, fairly well nourished white man, appearing chronically ill. There was an increase in the difficulty with hearing. No other abnormalities related to the head or neck were present. The chest and heart were normal on examination. The blood pressure was 130/80. The liver and spleen were not palpable. Numerous subcutaneous lesions were palpable, especially over the abdomen, both flanks of the right groin and the anterior portions of the thighs bilaterally. Another lesion was palpable beneath the left breast, and two new lesions were appearing in the right arm. Neurological examination disclosed an ataxic, staggering gait with weakness, the presence of Romberg's sign with weakness of the lower extremities and a decrease in the pain, light touch and vibratory sensation and in the position sensation in the lower extremities. The ankle jerks were absent. A questionable Babinski sign was noted on the right. These findings were suggestive of peripheral neuropathy combined with pathological involvement of the cord in the posterior and lateral columns, the etiological basis being obscure. The patient's temperature ranged from 102 to 103 F. Daily elevations occurred during a control period before cortisone was administered.

The patient's initial blood count disclosed anemia and leukopenia, with a hemoglobin value of 9.5 Gm., 3,500,000 red blood cells, 1,500 leukocytes, 67 per cent polymorphonuclear forms with 31 per cent nonfilamented cells, 27 per cent lymphocytes and 6 per cent monocytes. Urinalyses had normal results, and serologic reactions were negative. The serum proteins were 6.1 Gm., with 4.1 Gm. of albumin and 2 Gm. of globulin. The serum calcium was 7.5, 8.6 and 7.9 Gm. on three occasions; serum phosphorus was 3.9 mg. A dextrose tolerance curve showed a fasting sugar level of 109 mg., 143 mg. at one-half hour, 159 mg. at one hour, 128 mg. at two hours and 121 mg. at three hours. There was no reaction for sugar in the urine at any time. Serum alpha amino acids were 4.64 mg. of amino nitrogen per 100 cc. of serum. Blood urea nitrogen was 11 mg. Sodium was 145 and potassium 4.85 milliequivalents per liter. The 24 hour excretion of 17-ketosteroids was 1.6 mg. This determination was repeated and found to be 4.0 mg. Radioactive iodine uptake was found to be 23 per cent of the administered dose. Bone marrow examination revealed a hypoplastic marrow with a relative normoblastic hyperplasia. The water partition studies were carried out by Dr. Joan Long, and serum lipid fractionations were determined in the laboratory of Dr. H. Shay. These determinations will be reported subsequently.

The patient was placed on a diet containing 80 Gm. of protein and 2 Gm. of sodium chloride, with a total of 2,400 calories. Three hundred milligrams of cortisone was administered the first day and 100 mg. daily for 10 days. During this interval the patient's temperature returned to normal slowly over a period of seven days and remained normal for five days, with a concomitant reduction in the pulse rate. Following the discontinuance of cortisone administration, the temperature immediately rose again to daily spikes of 101 to 103 F. At this time a course of treatment with potassium paraaminobenzoate was administered. The initial dose used was 4 Gm., and 2 Gm. was given every four hours for two weeks. This drug was without effect on the course of the disease. Vitamin B_{12} was given in large doses for three weeks without altering the neurological or hematological abnormalities. Because of the hypocalcemic symptoms, the presence of Trousseau's sign and several low serum calcium values with normal serum inorganic phosphorus levels, investigations of the gastrointestinal tract by roentgenogram and stool examinations for fat were made. Roentgenograms of the hands, feet, spine and long bones were obtained. Urinary calcium excretion was qualitatively evaluated with Sulkowitch reagent. None of these studies showed any deviation from the normal. Roentgenograms disclosed normal mineralization with no evidence of the short metacarpals seen in pseudohypoparathyroidism.[17] The electrocardiogram was normal, while the electroencephalogram

17. Albright, F.; Burnett, C. H.; Smith, P. H., and Parson, W.: Pseudo-Hypoparathyroidism: An Example of Seabright-Bantam Syndrome, Endocrinology **30**:92-932, 1942.

showed a borderline slow record of little diagnostic significance. During cortisone therapy there was no appreciable change in the serum calcium levels or in the electroencephalogram. Administration of vitamin D, together with a high calcium diet supplemented with calcium gluconate, brought the serum calcium levels to 9.2 mg. per 100 cc. temporarily, with a loss of the symptoms of hypocalcemia. These symptoms recurred when use of vitamin D was discontinued, and serum calcium fell to 8.0 mg. per 100 cc.

The radioactive iodine uptake determination after cortisone treatment showed no change from the control values. There was no change in the dextrose tolerance curve during cortisone therapy. After cortisone treatment there was slight improvement in the bone marrow,

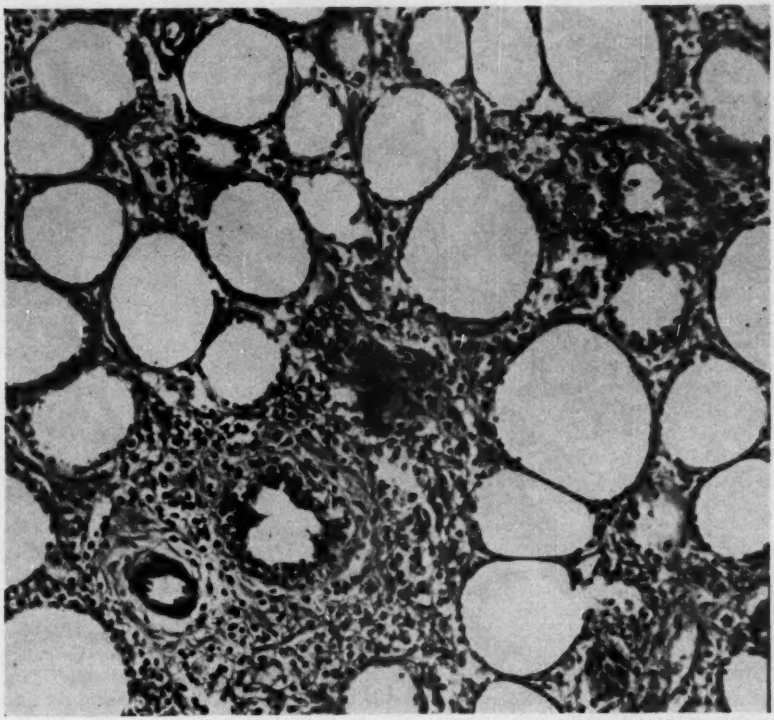

Fig. 1.—Section shows adult fat cells penetrated and surrounded by inflammatory cells. In one area there are two small vessels; one reveals endothelial proliferation, and the second shows inflammatory cells within the wall. Another small vessel is identified above and to the left of the aforementioned one; the wall of this vessel has a loose edematous appearance and an inflammatory cellular infiltration.

manifested by an increase in the myelocytes. However, no improvement in the peripheral blood picture was observed. Audiometric studies disclosed no change in the curves obtained before and after use of cortisone. A skin test using a fluorescein dye indicator showed that during the control period there was no inhibition of hyaluronidase following administration of epinephrine, suggesting hypoadrenocorticism.[18] However, when cortisone had been administered

18. Shuman, C. R., and Finestone, A. J.: Inhibition of Hyaluronidase in Vivo by Adrenal Cortical Activation, Proc. Soc. Exper. Biol. & Med. **73**:248-251, 1950.

for three days there was complete inhibition of the enzyme. Following the discontinuance of cortisone therapy, hyaluronidase inhibition again decreased and could not be produced by injections of epinephrine as during the trial period. During the subsequent interval of therapy with potassium paraaminobenzoate, hyaluronidase inhibition reappeared as determined by the aforementioned skin test. A repeated course of x-ray therapy was contemplated, as was a course of therapy with nitrogen mustard. However, because of the persistent severe neutropenia, the plans for such treatment were abandoned and the patient was discharged from the hospital. The patient refused to allow removal of subsequent biopsy specimens of the panniculitis lesions because of the difficulty encountered with healing following the previous removals.

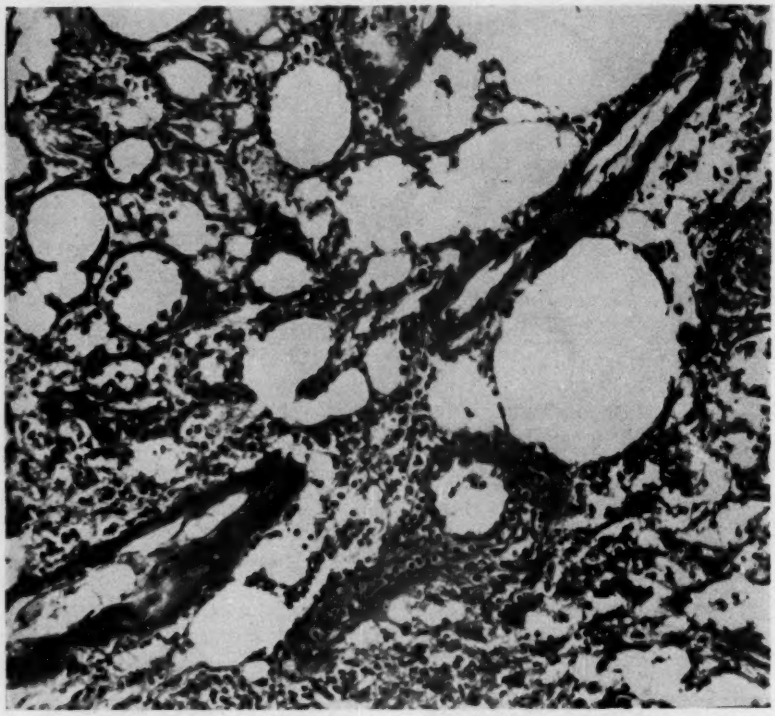

Fig. 2.—Microscopic section (× 200) demonstrating the subcutaneous fatty tissue sprinkled with inflammatory cells and showing two vessels, the walls of which reveal hyaline or fibrinoid necrosis. The vessel walls have a smudgy dark-staining appearance, and cell detail is lost.

The diagnoses at this time were (1) panniculitis of the Weber-Christian type with anemia and neutropenia, (2) hypocalcemic tetany, cause undetermined, (3) bilateral otosclerosis and (4) hypofunction of the adrenal cortex.

Third Admission (July 29 to Aug. 26, 1950).—The patient left the hospital in May feeling somewhat improved, although still experiencing daily febrile rises. Partial remission continued until July 15, 1950, when symptoms of fever, weakness and burning pains in the feet recurred. His gait became more unsteady, and he could not walk. On July 29 he was readmitted to the hospital. Examination showed no new lesions and no significant change in those present several months previously. Neurological examination disclosed a decrease in all

modalities of sensation in the legs. Achilles reflexes were absent, and the patellar tendon reflexes were diminished. The gait was ataxic; the legs were very weak, the right weaker than the left. A pseudo-Babinski sign was present on the right.

Daily rises in temperature to 103 F. were again noted. The patient seemed depressed and phlegmatic. Laboratory studies showed a persistent leukopenia (a count of 2,200 white blood cells), with 80 per cent polymorphonuclear cells, of which 68 per cent were nonfilamented forms. The hemoglobin content was 8.6 Gm. The urinalysis revealed no abnormality.

It was planned to provide treatment with pituitary adrenocorticotropic hormone (ACTH) and perhaps a course of x-ray therapy following multiple transfusions. While transfusions were being obtained for the patient, a course of salicylate therapy, 8 Gm. a day, was administered in an attempt at antipyresis. During the fourth day of salicylate therapy, the patient became disoriented and irrational. During the next three days he became unconscious, had several convulsions, exhibited pulmonary edema and died. On the last day of salicylate therapy, a determination of the carbon dioxide-combining power showed 53 volumes per cent; the serum sodium was 144 and serum potassium 4.5 milliequivalents per liter. Blood urea nitrogen and chlorides were also normal. A spinal tap prior to death showed normal pressure of 116 mm. of water; the spinal fluid cell count and chemical values were normal as on the tap done during the first admission. Permission for autopsy was not given by the family.

Histopathological Studies (Dr. A. R. Peale).—Biopsy specimens of the nodules were taken on two occasions by Dr. Robert Bucher. Sections of these tissues disclosed an intense infiltration of the adipose tissue with mononuclear cells, chiefly lymphocytes and macrophages, the latter manifesting a foamy vacuolated cytoplasm in many areas. In addition, neutrophils, eosinophils and plasma cells were identified. These cells distorted the fat lobules and surrounded individual fat cells; there was fat necrosis in some areas. The interlobular septums showed collagenous thickening with edema and fibrinoid alteration in some areas. Lymphoid cells in certain sections were large, with coarse chromatin markings, suggesting the possibility of lymphoma. In other places the polymorphic response was reminiscent of that of Hodgkin's disease, except that no Sternberg-Reed cells could be found. Giant cells were infrequent. The process appeared to be confined to fat, although there was some infiltration of mononuclear cells about the sweat and sebaceous glands.

Vascular reactions of two types were distinguished in these sections. Many of the small vessels showed inflammatory cellular infiltrations with endothelial swelling and thickening of the walls (fig. 1). Other vessels manifested a homogeneous pink stain resembling that seen in fibrinoid degeneration (fig. 2). There was a scanty inflammatory change around the nerves. The significance of these vascular and neural changes could not be assessed. They may simply have represented the response of these tissues to the surrounding inflammatory process. However, the possibility of hypersensitivity or vascular damage resulting from antigen-antibody reaction might be considered.

COMMENT

The onset of the disease in this patient was associated with trauma. However, the appearance of multiple nodules during his subsequent course with no associated trauma leaves doubt concerning the importance of the injury in the pathogenesis of the disease. The establishment of a source of abnormal products of lipolytic fat metabolism in an area of traumatized panniculus may account for changes occurring in fat elsewhere in the body. However, the search for such substances has been fruitless. In the present case, removal of specimens of the nodules for biopsy led to an extension of the lesions adjacent to the areas of the incision and to the appearance of new lesions.

Trauma has been recognized in the case of Baumgartner and Riva [19] as a cause of the reappearance of nodules in a patient during remission. Fraser [16b] has

19. Baumgartner, W., and Riva, G.: Pannikulitis, die herdförmige Fettgewebsentzündung, Helvet. med. acta (supp. 14) **12**:3-69, 1945.

recorded a case in which an injury was the apparent precipitating factor. Local trauma was present in the case of Miller and Kritzler.[6] Brill [11a] states that his patient was struck by a ball prior to the onset of her illness. The reactive process occurring in fat as a result of injury has been discussed by Smetana.[20] The lipogranulomatous change usually occurring at the site of an injury to the subcutaneous tissue resembles the pathological picture found in Weber-Christian disease but does not share the more widespread distribution of the lesion or the constitutional symptoms produced by this disease. Where trauma has not been recalled as a factor in panniculitis, it is possible that an injury was mild and instantly forgotten.

Therapy with halogens, chiefly bromides and iodides, has been repeatedly introduced as a factor causing Weber-Christian disease.[21] There was no history of ingestion of these agents in this case. The patient had not taken drugs in the past with any regularity. There was no allergic history.

The relationship of panniculitis to rheumatoid arthritis, fibrositis and other collagen diseases has been stressed by various authors.[22] There was no evidence of rheumatoid disease in the present case. The patient complained of pain in the feet which developed together with neurological changes indicative of peripheral neuropathy. Reflex neurovascular symptoms have been reported by Steinbrocker and his co-authors [23] in Weber-Christian disease.

Delay in the healing of biopsy sites has been found in many of the case reports.[24] In the present case the initial surgical incision failed to show healing for eight months, during which time a thin serous fluid drained from it. Culture of the fat was negative, but contamination of the wound occurred with Staphylococcus and Pseudomonas, which gradually disappeared. All other bacteriologic and serologic studies, as well as viral and animal inoculation procedures, gave negative results. Skin reactions for agents of viral and mycotic diseases were negative. Similar negative findings are noted in many of the reported cases.[25] Foci of infection have

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20. Smetana, H. F., and Bernhard, W.: Sclerosing Lipogranuloma, Arch. Path. **50**:296-325 (Sept.) 1950.

21. Netherton.[10c] Niedermayer and Moran.[9d] Tilden and others.[18d] Weber, F. P.: A Further Note on Relapsing Febrile Nodular Nonsuppurative Panniculitis, Brit. J. Dermat. **47**:230-235, 1935.

22. Alderson and Way.[16a] Bailey.[8a] Binkley.[9b] Brudno.[11b] Hazel, O. G., and Lamb, J.: Primary Panniculitis (Weber-Christian Disease) Afebrile in Type and Associated with Sclerodermatous-like Changes, J. Oklahoma M. A. **33**:1-5, 1940.

23. Steinbrocker, O.; Spitzer, N., and Friedman, H. H.: The Shoulder-Hand Syndrome in Reflex Dystrophy of the Upper Extremity, Ann. Int. Med. **29**:22-52, 1948.

24. Binkley.[9b] Brudno.[11b] Bunnell and Levy.[5b] Friedman.[8c] Hanson, W. A., and Fowler, L. H.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Minnesota Med. **24**:779-782, 1941.

25. Bailey.[8a] Hartwell, A. S., and Thannhauser, S. J.: Case Presentation and Discussion of Relapsing Febrile Nodular Nonsuppurative Panniculitis, Bull. New England M. Center **2**:362-368, 1940. Ives, G.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, with Report of a Case, J. Missouri M. A. **42**:409-410, 1945. Koster, L., and Behr, E.: Une forme speciale de la lipogranulomatose généralisée, Acta med. scandinav. **93**:30-41, 1937. Machacek, G. F.: Chronic Panniculitis of Unknown Source (Weber-Christian Disease?) (Relapsing Febrile [?] Nodular Nonsuppurative Panniculitis), Arch. Dermat. & Syph. **40**:473-474 (Sept.) 1939. Sweitzer, S.: Recurrent, Nonsuppurative, Nodular Panniculitis, ibid. **43**:216 (Jan.) 1941. Ziegert, H. J.: Ein Fall von fieberhafter Wucheratrophie des Fettgewebes (Weber-Christian'sche Krankheit), Zentralbl. inn. Med. **61**:610-612, 1940.

been mentioned as etiological factors; however, removal of such foci has not been helpful in management.[26] No such foci were found in this case.

Therapeutic trials were performed for long intervals with many drugs. These were outlined in the case history and included penicillin, streptomycin, aureomycin, sulfonamides, emetine and neoarsphenamine. There was no response in the febrile course or toxicity during the exhibition of these antimicrobial agents. In previous reports cultures yielded organisms including Streptococcus,[27] Staphylococcus [28] and Mycobacterium tuberculosis,[13d] but there is no evidence that any of these is causative. Previous reports of response to penicillin,[29] neoarsphenamine [8e] and sulfonamide [9a] therapies have not been confirmed.

Evaluation of the adrenal cortex function was made on several occasions. Evidence of reduced activity was found in the following data: (1) low 17-ketosteroid excretion, (2) positive reactions to Robinson-Power-Kepler tests on two occasions and (3) absence of hyaluronidase inhibition on skin test following epinephrine administration.[18] During cortisone administration hyaluronidase was greatly inhibited as measured by fluorescein dye. The response of eosinophils to epinephrine administration could not be used, as all control counts were negative because of bone marrow depression. It was felt that hypoadrenocorticism was an effect of the long-standing febrile process rather than a cause of the disease. The response to treatment with cortisone was only partial and brief in duration.

Evaluation of gonadal function was also important, inasmuch as one of the patient's initial symptoms, before the skin lesions were noticed, was loss of libido. No gross changes in the testes were palpable, and a biopsy specimen was not obtained. However, when a remission appeared in the disease following x-ray therapy, there was a prompt return of libido, and the patient experienced erections for the first time since the onset of the illness. Libido disappeared within two months when a relapse occurred. Because of this, large amounts of testosterone propionate were used in treatment for three months without influencing the disease.

The function of the thyroid gland was studied with I^{131} uptake and found to be normal. This rate of iodine uptake was not disturbed during treatment with cortisone. There was no clinical basis on which to suspect pancreatic disease. The dextrose tolerance curve was normal. Amylase and lipase determinations were not obtained.

The development of hypocalcemic symptoms with tetany after approximately one year of illness is an unusual feature of this case. The possibility of Seabright bantam syndrome was considered because of the physical characteristics of the patient.[17] Response of the symptoms and of the serum calcium levels was satisfactory on treatment with calcium lactate and vitamin D. Either hypofunction of the parathyroids or end organ unresponsiveness to their hormone seemed likely, though unproved.

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26. Skiöld, N.: Relapsing Febrile Nonsuppurative Panniculitis: Report of Case, Acta med. scandinav. **105**:43-47, 1940.

27. Alderson and Way.[16a] Ungar.[13b]

28. Puente, J. J.: Paniculitis nodular recidivanté febril de origen estafilocóccico: Un caso de granuloma lipofágico de la mama, Rev. uruguaya de dermat. y sif. **3**:52, 1938.

29. Zee, M. L.: Nodular Nonsuppurative Panniculitis Treated with Penicillin, J. A. M. A. **130**:1219-1220 (April 27) 1946.

In the treatment of this patient the use of cortisone was instituted with high expectations for success, as it has been suggested that panniculitis may represent a form of collagen disease. The ameliorative effect of the hormone on granulomatous processes suggested that it would be beneficial in this disease. However, in 10 days of treatment there was little effect until the eighth day, when the temperature returned to normal. There was no alteration in the size of the lesions. The temperature remained normal for five days and then returned to previous levels of 103 F. after the cessation of cortisone therapy. ACTH administered during the last few days prior to death likewise showed no effect. The failure of large amounts of testosterone to modify any aspect of the disease has already been mentioned. Furthermore, extensive trials of cortisone and ACTH may be worthy of consideration. Antihistaminic therapy with tripelennamine for several weeks did not influence the clinical picture. Paraaminobenzoate (potassium) administration was of no benefit. This drug was found to inhibit hyaluronidase injected into the skin.

Supportive therapy with a high protein and high calory diet and vitamin supplementation, including vitamins of the B complex, B_{12}, D and C, maintained the patient in reasonably good nutritional status except for the development of seborrhea and polyneuropathy. Administration of large amounts of iron, protein and testosterone failed to influence the anemia. Leukopenia and bone marrow hypoplasia were unaffected. Salicylates were given during the final week of the illness, which may have been an aggravating factor in the terminal mental picture of confusion, restlessness and coma. However, the patient appeared desperately ill prior to their administration.

The analysis in this case indicates that Weber-Christian disease is not of an infectious origin, although possibility of a viral agent has not been entirely excluded. The possibility of the disease being produced by metabolic derangements occurring in the fat must be entertained. Studies engaged in in examining this line of reasoning have not yet been productive. The relationship of this disease to other clinical entities, such as Whipple's [30] disease, erythema nodosum,[31] adiposis dolorosa, lipogranulomas associated with insulin or other injections and scleroderma, is not known, but it is clinically distinct despite histopathological similarities.

The report of Hodgkin's disease in two cases is an important fact which requires further scrutiny. One additional case [7b] was originally designated Hodgkin's disease, a diagnosis which was retracted in favor of the one of panniculitis. Clinically the disease has many features of Hodgkin's disease. If fat tissue is to be regarded as an organ derived from the mesenchyma and closely related to reticuloendothelium, being of the same derivation,[32] there is some justification for relating these two diseases more closely. The response of the present patient to initial x-ray therapy was quite as dramatic as that seen in the treatment of Hodgkin's disease. The gradations of severity of the two diseases are also similar, the milder cases corre-

30. Hendrix, J. P.; Black-Schaffer, B.; Withers, R. W., and Handler, P.: Whipple's Intestinal Lipodystrophy: Report of 4 Cases and Discussion of Possible Pathogenic Factors, Arch. Int. Med. **85**:91-131 (Jan.) 1950.

31. Rist, E., and Renault, P.: Erythème induré récidivant ou maladie de Weber-Christian? Bull. et mém. Soc. méd. hôp Paris **63**:515-523, 1947.

32. Wertheimer, E., and Shapiro, B.: The Physiology of Adipose Tissue, Physiol. Rev. **28**:451-464, 1948.

sponding to Hodgkin's paragranuloma or granuloma with a duration of many years, in contrast to the severe cases which progress rapidly as does Hodgkin's sarcoma. The pathological aspects of the two diseases are not entirely dissimilar, although Sternberg-Reed cells are not found in panniculitis.

The fibrinoid degeneration in the interlobular areas and in the vessel walls (fig. 2)[33] no doubt represents a form of nonspecific tissue response to a local inflammatory process. However, this type of histopathological alteration is also found in the so-called collagen diseases in which hypersensitivity is regarded as a pathogenic factor. Further studies scrutinizing antigen-antibody reactions in these patients are indicated.

CONCLUSIONS

A fatal case of relapsing panniculitis (Weber-Christian disease) is presented, with a discussion of studies and therapeutic trials conducted over a period of 21 months, from the onset of the disease until the death of the patient. The illness was associated with widespread nodular involvement of the subcutaneous panniculus and high fever.

Remission was induced on one occasion for two months with x-ray therapy. Subsequent treatment failed to alter the course of the disease. Cortisone therapy succeeded in producing a normal temperature for five days.

A reduction of adrenal cortex function was suggested by the finding of low 17-ketosteroid excretion, positive reactions to Robinson-Power-Kepler tests and failure of hyaluronidase inhibition after epinephrine administration. Hypocalcemic symptoms occurred during the course of the disease and responded to calcium and vitamin D therapy.

The relationship of Weber-Christian disease to other disease entities is briefly discussed.

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33. Bailey.[8a] Cummins and Lever.[13b] Niedermayer and Moran.[9d]

CLINICAL ASPECTS OF DIETARY DEPLETION OF RIBOFLAVIN

O. W. HILLS, M.D.
ROCHESTER, MINN.
E. LIEBERT, M.D.
CHICAGO
D. L. STEINBERG, M.D.
AND
M. K. HORWITT, Ph.D.
ELGIN, ILL.

THE CONCEPT of riboflavin deficiency in man as a syndrome characterized by angular stomatitis, a sore, magenta tongue, seborrheic dermatitis about the nose and scrotum and vascularization of the cornea has been generally accepted since the publication of the findings of Sebrell and Butler [1] in 1938. In general these confirmed earlier reports by Stannus [2] and other observers. However, review of the various diets and circumstances suggests that multiple vitamin and amino acid deficiencies were involved. It was the purpose of this study to attempt to create and study a pure riboflavin deficiency in controlled circumstances. A summary of this project,[3] an analysis of the urinary excretion of riboflavin [4] and a description of the dietary management of such a study [5] have previously been reported. The present paper is chiefly concerned with the clinical findings.

HISTORICAL REVIEW

The first description of the clinical findings, which have subsequently become known as ariboflavinosis, was published by Stannus in 1911,[2] 25 years before

From the Elgin State Hospital.
United States Public Health Service Senior Fellow 1947 (Dr. Hills).

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1. Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man, Pub. Health Rep. **53**:2282, 1938.

2. Stannus, H. S.: Pellagra in Nyasaland (Second Communication), Tr. Roy. Soc. Trop. Med. & Hyg. **7**:32, 1913.

3. Horwitt, M. K.; Hills, O. W.; Harvey, C. C.; Liebert, E., and Steinberg, D. L.: Effects of Dietary Depletion of Riboflavin, J. Nutrition **39**:357, 1949.

4. Horwitt, M. K.; Harvey, C. C.; Hills, O. W., and Liebert, E.: Correlation of Urinary Excretion of Riboflavin with Dietary Intake and Symptoms of Ariboflavinosis, J. Nutrition **41**:247, 1950.

5. Horwitt, M. K.; Sampson, G.; Hills, O. W., and Steinberg, D. L.: Dietary Management in a Study of Riboflavin Requirements, J. Am. Dietet. A. **25**:247, 1950.

riboflavin itself was discovered. His findings were confirmed and augmented by Bahr [6] (1912 to 1914) in Ceylon, Scott [7] (1918) in Jamaica, Moore [8] (1930 and 1939) in West Africa, Landor and Pallister [9] (1935) in Singapore, Aykroyd and Krishnan [10] (1936) in South India and Goldberger, Wheeler [11] and Tanner [12] (1920 and 1925) in the United States. It was generally recognized that the lesions were on the basis of some dietary deficiency and that they could be cured by administration of vitamin B complex. The isolation of the "yellow enzyme" by Warburg and Christian [13] in 1932 and its subsequent recognition by Kühn [14] in 1933 as a vitamin of the B complex laid the groundwork for the experimentally produced riboflavin deficiency of Sebrell and Butler [1] mentioned above. Their diet contained 0.5 mg. of riboflavin per day. Lesions of the skin of the mouth were neither prevented nor cured by the administration of thiamine or nicotinic acid but yielded readily to riboflavin treatment. Lesions of the eye, in particular corneal vascularization, were described in the rat by Bessey and Wolbach [15] in 1939 and by Spies [16] (1939), Sydenstricker [17] (1939) and Kruse [18] (1940) in the human being. Extensive corneal vascularization among members of the Royal Canadian Air Force which seemed to respond to riboflavin administration was observed by Tisdall, McCreary and Pearce [19] in 1943.

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6. Bahr, P. H.: A Report on Researches on Sprue in Ceylon, 1912-1914, London, Cambridge University Press, 1915.

7. Scott, H. H.: An Investigation into an Acute Outbreak of Central Neuritis, Ann. Trop. Med. **12**:109, 1918.

8. Moore, D. G. F.: Partial Loss of Central Acuity of Vision for Reading and for Distance in School Children and Its Possible Association with Food Deficiency, West African M. J. **4**:46, 1930; Retrobulbar Neuritis with Pellagra in Nigeria, J. Trop. Med. **42**:109, 1939.

9. Landor, V. J., and Pallister, R. A.: Avitaminosis B_2, Tr. Roy. Soc. Trop. Med. & Hyg. **19**:121, 1935.

10. Aykroyd, W. R., and Krishnan, B. G.: Stomatitis Due to Vitamin B_2 Deficiency, Indian J. M. Research **24**:411, 1936.

11. Goldberger, J., and Wheeler, G. A.: Experimental Production of Pellagra in Human Subjects, Hygienic Laboratory Bulletin no. 120, United States Treasury Department, Public Health Service, 1920, p. 116.

12. Goldberger, J., and Tanner, W. F.: A Study of the Pellagra Preventive Action of Dried Beans, Casein, Dried Milk, and Brewers' Yeast, Pub. Health Rep. **40**:54, 1925.

13. Warburg, O., and Christian, W.: Über ein neues Oxydationsferment und sein Adsorptionsspektrum, Biochem. Ztschr. **254**:438, 1932.

14. Kühn, R.; György, P., and Wagner-Jauregg: Über Ovoflavin, den Farbstoff des Eiklars, Ber. d. deutsch. chem. Gesellsch. **66**:576, 1933.

15. Bessey, O. A., and Wolbach, S. B.: Vascularization of the Cornea of the Rat in Riboflavin Deficiency with a Note on Corneal Vascularization in Vitamin A Deficiency, J. Exper. Med. **69**:1, 1939.

16. Spies, T.; Vilter, R. W., and Ashe, W. F.: Pellagra, Beriberi and Riboflavin Deficiency in Human Beings: Diagnosis and Treatment, J. A. M. A. **113**:931 (Sept. 2) 1939. Spies, T. D.; Bean, W. B., and Ashe, W. F.: Recent Advances in the Treatment of Pellagra and Associated Deficiencies, Ann. Int. Med. **12**:1830, 1939.

17. Sydenstricker, V. P.; Geeslin, L. E.; Templeton, C. M., and Weaver, J. W.: Riboflavin Deficiency in Human Subjects, J. A. M. A. **113**:1697 (Nov. 4) 1939.

18. Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H., and Cleckley, H. M.: Ocular Manifestations of Ariboflavinosis, Pub. Health Rep. **55**:157, 1940.

19. Tisdall, F. F.; McCreary, J. F., and Pearce, H.: The Effect of Riboflavin on Corneal Vascularization and Symptoms of Eye Fatigue in R. C. A. F. Personnel, Canad. M. A. J. **49**:5, 1943.

Subsequent efforts with isolated restriction of riboflavin to reproduce the results obtained by Sebrell and Butler,[1] using somewhat more liberal allowances of riboflavin, have not been successful. Williams, Mason, Cusick and Wilder[20] (1943) fed a diet containing between 0.8 and 0.9 mg. (0.35 mg. per 1,000 calories) of riboflavin per day for over nine months, and Keys, Henschel, Mickelsen, Brozek and Crawford[21] (1944) gave 1.0 mg. (0.3 mg. per 1,000 calories per day) for five months. Neither study revealed any clinical changes. Horwitt, Liebert, Kreisler and Wittman[22] (1948) fed a diet containing between 0.8 and 0.9 mg. of riboflavin daily for over two years, and only one of 22 subjects showed any signs (angular stomatitis) that might be attributed to a lack of riboflavin. In all these studies the urinary excretion of riboflavin was reduced to minimal levels, yet no definite dermatological signs as noted by Sebrell and Butler[1] (1938) and the others could be observed.

PRESENT STUDY

The lesions heretofore attributed to deficiency of riboflavin have been observed under clinical conditions in which deficiencies of several essential nutrients coexisted, response to riboflavin supplementation and failure of response to other therapy being the sole criteria for the diagnosis of a state of riboflavin deficiency. Pure riboflavin deficiency may differ considerably, or even not exist at all, as a clinical entity, and the etiological basis of the lesions one observes may actually be multiple, including not only deficiencies of other vitamins but also the effects of the environment.

In the present study an attempt was made to supply the subjects with a diet adequately supplemented with all known essential nutrients and deficient only in riboflavin. Also the persons studied, as hospital patients living in a group, were subjected to almost identical environmental circumstances at all times.

Thirty-nine patients of the hospital with a mental disorder of the schizophrenic group were chosen for this study. All were men. The range in age was 18 to 48 years. The selection was made on the basis of excellent physical condition, fairly good emotional stability observed over a period of years and the probability of prolonged hospitalization. The subjects and their relatives had given their consent to the project. All were housed in a special building with a diet kitchen and laboratories. Prior to the beginning of the experimental period, a three month feeding trial was instituted in order to observe and train the subjects and obtain some basic data.

The trial diet contained 1.1 mg. per day of riboflavin and the experimental diet 0.55 mg. per day. The latter figure was chosen because of the positive findings of Sebrell and Butler[1] when they gave 0.5 mg. of riboflavin per day and the negative findings of other investigators giving larger amounts, but we found it difficult to devise a reasonably palatable diet for long term consumption containing less than 0.55 mg. per day.

In May 1947 the experimental period started. Fifteen of the 39 subjects (group A) received the diet containing 0.55 mg. of riboflavin per day. Fourteen subjects (group B) received the same diet as group A but, in addition, were given a daily supplement of 2 mg. of riboflavin orally. Ten subjects (group C) were allowed to eat without restriction the regular hospital diet, which contained about 1.6 mg. of riboflavin.

Diet.—The basic diet provided 2,200 calories, 57 Gm. of protein, 65 Gm. of fat and 0.55 mg. of riboflavin per day. The natural food provided less than 45 Gm. of protein, but this was

20. Williams, R. D.; Mason, H. L.; Cusick, P. L., and Wilder, R. M.: Observations on Induced Riboflavin Deficiency and the Riboflavin Requirements of Man, J. Nutrition **25**:361, 1943.

21. Keys, A.; Henschel, A. F.; Mickelsen, O.; Brozek, J. H., and Crawford, J. H.: Physiological and Biochemical Functions in Normal Young Men on a Diet Restricted in Riboflavin, J. Nutrition **27**:165, 1944.

22. Horwitt, M. K.; Liebert, E.; Kreisler, O., and Wittman, P.: Investigation of Human Requirements for B-Complex Vitamins, National Research Council Bulletin no. 116, Washington, D. C., National Academy of Sciences, 1948.

supplemented with 10 to 12 Gm. of riboflavin-free calcium caseinate. No food from outside sources was permitted. The subjects consumed varying percentages of the basic diet depending on caloric requirements, their weights remaining constant. The amounts taken were carefully recorded.

Supplemental vitamins [23] were given to every one in the A and B groups. The supplement contained 0.6 mg. of thiamine hydrochloride, 10 mg. of nicotinamide, 0.1 mg. of folic acid, 50 mg. of ascorbic acid, 4,000 U. S. P. units of vitamin A and 400 U. S. P. units of vitamin D. In addition, 500 mg. of dicalcium phosphate was given daily and 180 mg. of ferrous sulfate three times weekly. An analytical control of the riboflavin content of the diet was made at frequent intervals. About one half of all the meals were sampled and assayed, and no disturbing deviation from the desired quantities was found.

Methods.—Before discussing the results of the experiment, it seems desirable to mention certain aspects that were emphasized, and to list examinations made. Most of these did not show any appreciable abnormality and will not be dealt with in detail. Based on the reports in the literature previously cited, our studies were directed especially toward examination of the skin, the tongue, the eyes, the capillary bed, the central and peripheral nervous systems and the biochemical values for the blood and urine.

General laboratory examinations performed at regular intervals during the experimental period were the determination of the hematocrit, hemoglobin concentration, erythrocyte, leukocyte and differential blood count, erythrocyte sedimentation rate and basal metabolic rate, electrocardiographic tracing and roentgenograms of the chest and heart. Cephalin flocculation tests, icteric indexes and blood cholesterol, phospholipid, nonprotein nitrogen and creatinine values were obtained during special phases of the study. The response of the pulse rate to rest and exercise was followed closely throughout the experimental period.

The skin was studied by observation, and photographs were made of local areas, such as the oral angles, lips and scrotum. In addition, skin resistance, as measured by the ohmmeter and the Wheatstone bridge, was estimated frequently in selected areas. Wound healing was investigated in rats fed the same diet as that given to the subjects.

The appearance of the tongue was recorded by color photography and also by prints utilizing methylene and Evans blue dyes.

The eyes were followed with particular care because of conflicting opinions concerning the development of corneal vascularization in riboflavin deficiency. Slit lamp examinations were conducted at monthly intervals by Dr. Orville E. Gordon, of Dr. Derrick Vail's ophthalmological staff at Northwestern University. The findings were objectively documented by photographic records following application of 1 per cent solution of ethylmorphine hydrochloride (dionin®) into the conjunctival sac. Secretion of the lacrimal glands was measured by the Schirmer [24] test, and corneal sensitivity was tested with nylon fibers of varying tensile strength.[25] Other visual tests will be mentioned under studies of the central nervous system.

The state of the central nervous system was judged by general patterns, such as attitude, behavior, appetite, psychological performance and fatigue test reactions, and more specifically by results of visual acuity and audiometer examination. The last was performed with the Maico audiometer. Vision was analyzed by standard reading tests, by having the patient compare the brightness of a rheostat-controlled light bulb with a light of standard intensity, by the ability to distinguish flicker as measured with a flickering neon bulb and by adaptation to the dark. The neon light controlled by an oscillating tube enables one to attain complete extinction between flashes, the subject being seated at a distance of 6 feet (183 cm.) from the light source. An instrument was designed for testing adaptation to the dark. After a half-hour in a dark room, the subject is asked to read numbers flashed on a screen with varying intensities of light.

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23. This preparation was a special formula supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

24. Cited by de Rötth, A.: On Hypofunction of Lacrimal Gland, Am. J. Ophth. **24**:20, 1941.

25. Supplied by E. I. DuPont de Nemours Co., Arlington, N. J.

The condition of the peripheral nerves was followed by means of routine examinations. Objective measurements of the vibration sense, the achilles tendon reflex and Romberg's sign were made with the aid of special instruments.

The state of the circulation and capillary bed was followed by means of the finger plethysmograph, the skin temperatures of the hands and photographs of the capillaries of the nail bed.

The 24 hour urinary excretion of riboflavin and the excretion of riboflavin during a four hour period following the injection of 0.1 mg. of riboflavin were studied at three monthly intervals. The blood riboflavin was estimated according to a microbiologic method similar to that of Strong, Feeney, Moore and Parsons.[26] The "double metabolic load" recommended by Horwitt, Liebert, Kreisler and Wittman [22] was applied to the evaluation of blood lactic and pyruvic acid levels.

RESULTS

The positive findings will be described first, followed by the important negative determinations and, finally, by representative case histories.

The outstanding pathological findings were those observed in the skin [27] of the 15 subjects of group A, receiving 0.55 mg. of riboflavin daily. One subject (case 1) displayed seborrhea of the scalp and chest, scrotal dermatitis, angular stomatitis (fig. 1 *A*) and fissuring of the alae nasi. The first of any of these lesions was noted 4½ months after the inception of the deficient diet. A second and a third subject showed angular stomatitis, a fourth a seborrheic patch over the left mastoid region and a fifth a similar patch about the base of the nostril. The seborrhea was always patchy in distribution rather than confluent and was dry and scaly rather than greasy. There was no pyoderma or fungous infection. Pruritus was usually present.

Cheilosis, involving the vermilion border of the lips and including vertical fissuring, crusting and desquamation of the mucous membrane, was seen in a sixth subject. In his case the lesion was never more than minimal and was manifested by redness and superficial vertical fissuring in a lip that was naturally almost abnormally protuberant. Angular stomatitis is defined as the crusting and fissuring of the skin of the oral angles—not crossing the vermilion border. In none of the three subjects with this condition was there any evidence of excessive salivation or inefficient dentures. In case 1 a bacteriologic investigation of the wound failed to produce evidence of a mycotic infection.

The lesion seen most frequently was the dermatitis of the scrotum. Twelve of the 15 subjects on the deficient diet (group A) had it either mildly or severely (fig. 1). Typically this began as a patchy redness associated with scaling and desquamation of the superficial epithelium of the anterior surface of the scrotum bilaterally. The median commissure at all times remained uninvolved. The more prolonged and severe cases showed a lichenification of the involved areas. In one subject (case 2) a raw and weeping lesion rapidly developed and extended to the inner aspect of the adjacent thighs. This was painful. The lesions in the other subjects were associated with only mild symptoms of burning and itching or, more commonly, with no symptoms at all.

The course of all the dermatological eruptions was one of exacerbations and remissions. The scrotal lesions in several subjects and two or three of the oral and nasal fissures healed spontaneously in the course of days or weeks and did

26. Strong, F. M.; Feeney, R. E.; Moore, B., and Parsons, H. T.: Riboflavin Content of Blood and Urine, J. Biol. Chem. **137**:363, 1941.

27. Dr. Cleveland J. White and Dr. H. S. Steinberg gave dermatological advice.

Fig. 1.—*A*, bilateral fissures of angular stomatitis in case 1. *B*, scaling, pruritic dermatitis on an erythematous base involving only the anterior aspect of the scrotum bilaterally in case 1. *C*, erythema in case 2, with lichenified and violaceous skin over the anterior aspect of the scrotum. *D*, erythema and superficial scaling of the scrotum in case 3 without involvement of the medial commissure.

not recur. The response to treatment with riboflavin of all subjects in whom the lesions had failed to heal spontaneously was prompt, and in two with severe scrotal inflammation the response was dramatic. The dose was 6 mg. per day, and healing was apparent within 48 hours and almost complete within a week. One subject (case 1) who had multiple manifestations showed rapid and complete healing of all his lesions on treatment with riboflavin, except for a patch on the scalp and the stomatitis at the left oral angle. Healing was delayed in these areas for several weeks by the patient's habit of picking or scratching.

Some weeks after these lesions had appeared in members of group A, three subjects in group B (who received the deficient diet supplemented with 2 mg. of riboflavin daily) displayed scrotal erythema with little or no scaling. This prompted an investigation of several hundred other hospital patients, who presumably were adequately nourished (the average hospital diet containing about 1.6 mg. of riboflavin daily). Scrotal erythema without scaling was found in a large percentage of incontinent patients or those who were quite careless about personal hygiene. It was felt that the basic skin irritation in all the patients showing this change was due to poor hygiene. A possible explanation for the severer manifestations in the riboflavin-deficient subjects will be discussed subsequently. This concept of an external irritant was further borne out by the failure of very large doses of riboflavin to alter the appearance of the scrotum in the three subjects in group B.

Because of the universality of the scrotal involvement in our subjects, a digression at this time for comparison with other reports seems pertinent. Only in recent years has the implication that scrotal dermatitis may be due to a deficiency of riboflavin gained much favor (Sydenstricker [28] and Purcell [29]), and even then it has been regarded as a relatively uncommon manifestation. However, the early literature on pellagra contains many references to scrotal dermatitis. Deiaco [30] in 1905 and Stannus [2] in 1913 mentioned such a lesion, and Stannus was the first to record that scrotal involvement may be the initial sign of developing deficiency (19 of 100 cases of pellagra). The most striking description, however, is that of Goldberger and Wheeler [11] in their classic report of the Rankin Prison Farm experiment. On a pellagra-producing diet six of their 11 patients exhibited scrotal dermatitis before any dermal lesions of pellagra appeared. A seventh subject showed only scrotal erythema and no other dermal lesions. Photographs and descriptions of these scrotal changes establish beyond a doubt that their findings were identical with those we have just described, viz., "bilaterally symmetrical scaly lesions separated by a median band of normal skin" (see fig. 2). The eruptions in Goldberger's patients appeared five months after the subjects had been on a diet containing approximately 0.58 mg. of riboflavin daily.[31] Our patients on a diet containing 0.55 mg. per day evolved their dermatitis in five to eight months. Whether

28. Sydenstricker, V. P.: The Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra), Ann. Int. Med. **14**:1499, 1941.

29. Purcell, F. M.: Nutritional Glossitis and Vitamin B_2 Therapy, Tr. Roy. Soc. Trop. Med. & Hyg. **35**:323, 1942.

30. Deiaco, P.: Beitrag zur Symptomatologie der Pellagra, Wien. klin. Wchnschr. **17**:908, 1905.

31. Frazier, E. I., and Friedemann, T. E.: Pellagra, A Study in Human Nutrition: Multiple-Factor Principle of Determination of Minimum Vitamin Requirements, Quart. Bull., Northwestern Univ. M. School **20**:24, 1946.

similar pathological changes might result from deficiency of nicotinic acid or its precursors without deficiency of riboflavin is now a subject of investigation.

Wound healing in deficiency of riboflavin was studied by us in growing rats, as has previously been reported.[3] In summary, duplicate wounds in rats fed the same diet as the human subjects healed completely in 20 days in the group whose diet was supplemented but were still evident after 54 days in animals whose diet was deficient in riboflavin. This is similar to the findings of Bosse and Axelrod [32] in rats on an even more deficient diet.

Studies of urinary excretion were made at dietary levels of 0.55, 0.75, 0.85, 1.1, 1.6, 2.15, 2.55 and 3.55 mg. per day of riboflavin.[4] Data were obtained on 24 hour urine samples and on samples obtained during the four hours after subcutaneous administration of 1 mg. of riboflavin. The results of the 24 hour excretion and of excretion during four hours after the giving of 1 mg. of riboflavin paralleled each other. Subjects exposed to little or no trauma or stress, as in the conditions of our experiment, and receiving 1.6 mg. of riboflavin per day, excreted

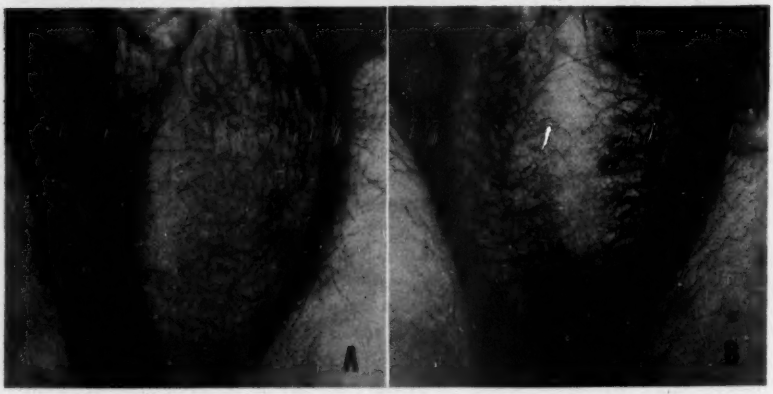

Fig. 2.—*A*, early scrotal dermatitis. *B*, "bilaterally symmetrical scaly lesions separated by a median band of normal skin."

four times as much riboflavin as those on an intake of 1.1 mg. This suggests that the critical riboflavin requirement for an adult male subsisting thus on 2,200 calories is somewhere between 1.1 and 1.6 mg. of riboflavin per day, and, as we stated before,[4] it is apparently impossible for the organism to store riboflavin at intakes of less than 1.1 mg. Also in our previous report we concluded that a 24 hour excretion of riboflavin measuring less than 100 mg. indicates that the diet is deficient in riboflavin, and that an excretion of less than 50 mg. indicates the deficiency has existed for some time and that symptoms are to be expected.

On the other hand, supplementation studies revealed that a depleted patient could assimilate at least 6 mg. of riboflavin at one time and that about 15 days would be required to saturate a severely depleted subject when a daily supplement of 6 mg. was given.[4]

32. Bosse, M. D., and Axelrod, A. E.: Wound Healing in Rats with Biotin, Pyridoxin or Riboflavin Deficiencies, Proc. Soc. Exper. Biol. & Med. **67**:418, 1948.

The important negative findings under the conditions of our study were as follows: First, no evidence of circumcorneal injection or vascularization of the cornea was seen at any time.[33] The tendency of small vascular twigs in the margins of the cornea to disappear and reappear months later was frequently noted, but no proliferation of the vessels of the limbic plexus was seen. Also no other ocular abnormalities were noted except for a tendency on the part of three subjects in the deficient group to lose the power to distinguish flicker. Further study of the significance of this behavior is necessary.

Secondly, none of our subjects had any evidence of glossitis. There was nothing to suggest "magenta" tongue, "red" tongue or loss of the normal papillae.

Thirdly, studies of the capillary bed mentioned earlier failed to reveal any evidence of a "capillary dyskinesia," suggested by Stannus [34] to be the fundamental pathological change of hyporiboflavinosis. None of the results of these tests in themselves is entirely satisfactory, but taken as a group they are suggestive that no significant changes took place in the general capillary bed.

There were no neurological abnormalities, and no change of attitude, activity or appetite, such as appears in thiamine deficiency,[22] was noted.

Biochemically there was a sharp contrast between the behavior of these subjects and that of those exposed to deficiency of thiamine as previously reported,[34a] in that the "double metabolic load" of glucose plus exercise failed to reveal any abnormality of the levels of lactic and pyruvic acids in the blood. This was surprising because of the intimate role played by both these vitamins in the enzyme systems involved in the metabolism of carbohydrate.

Finally, it should be noted that three subjects failed to display any clinical signs of riboflavin deficiency in spite of 15 months on the depleted regimen.

REPORT OF CASES

Three case reports are included in some detail to show the course of events in individual instances.

CASE 1.—A 30 year old white man, physically without any defects, with the psychiatric diagnosis of schizophrenia, hebephrenic type, had been in the institution for 3½ years prior to May 1947. He was at times somewhat irritable but usually quiet, cooperative and quite alert. He was rather shy in his conversation but always answered questions relevantly and coherently. After the termination of this project, he showed sufficient psychiatric improvement to permit a discharge from the institution, probably owing to the fact that during the nutritional study a great amount of indirect psychotherapy was afforded him. In February 1947 his physical status was normal. He was described as a well developed and well nourished red-haired man, with a clear complexion except for some freckles over his nose. Four and one-half months after the start of the depletion diet, a small herpes simplex lesion developed in the left oral angle. The herpetiform appearance of the lesion soon vanished, and it persisted as a typical fissure of angular stomatitis without involving the buccal mucous membrane. Shortly afterward two small patches of seborrhea appeared in the scalp and were resistive to treatment with unguentum sal-sulfur (composed of 1 Gm. of salicylic acid, 2 Gm. of precipitated sulfur and

33. Vail, D., and Ascher, K. W.: Corneal Vascularization Problems, Am. J. Ophth. **26**:1025, 1943.

34. Stannus, H. S.: Some Problems in Riboflavin and Allied Deficiencies, Brit. M. J. **2**:103 and 140, 1944.

34a. Horwitt, M. K., and Kreisler, O.: The Determination of Early Thiamine-Deficient States by Estimation of Blood Lactic and Pyruvic Acids After Glucose Administration and Exercise, J. Nutrition **37**:411, 1949.

petrolatum to make 30 Gm.). No therapy was applied to the mouth. Six weeks later a similar lesion appeared at the right oral angle without any preceding herpes infection (fig. 1 *A*). Smears and cultures of these lesions for monilia and other fungi were negative. Treatment with zinc oxide ointment and later with camphor liniment was then instituted. The lesion at the right oral angle healed in about three weeks and did not recur. The one on the left side continued in a fluctuating state of exacerbation and remission for several months. Two months after the first appearance of the angular stomatitis the patient contracted a mild infection of the upper respiratory tract, following which vertical fissures appeared at the tip of the nostrils. Subsequently, the inflammation of the right nostril spread as a weeping, crusty lesion over the anterior portion of the skin of the septum, followed by the appearance of a fissure at the right nasolabial fold. The fissure at the tip of the left nostril healed rapidly and spontaneously, but in January, two months later, a fissure formed at the left nasolabial fold. Also early in the same month, a scaling, pruritic dermatitis on an erythematous base appeared on the scrotum (fig. 1 *B*). Only the anterior aspect was involved bilaterally, and the medial commissure remained normal.

At this time it was thought that supplementation with riboflavin would be of diagnostic value, as the lesions had been present for over four months and were slowly progressing in spite of frequent temporary remissions. The picture was complicated by the patient's habit of scratching the affected areas. On Jan. 14, 1948, 6 mg. of riboflavin was added to the diet daily. The improvement of the scrotal lesion was prompt and unequivocal. The scaling and itching disappeared in less than a week, and the lesion could be considered entirely healed in two weeks' time except for a slight residual erythema. The healing of the more chronic lesions about the mouth, nose and scalp was not as dramatic but was also very definite. Over a 30 day period the scalp and nostrils healed completely with no change in local therapy. These lesions had been present for two to four months previously. The fissure at the left oral angle, which was the first to appear, was also the slowest to heal. The patient continued to excoriate this area, and fresh herpetic vesicles appeared on two occasions. Complete and permanent healing was not achieved until the middle of May—four months after the beginning of riboflavin supplementation and eight months after the first appearance of the angular stomatitis.

Case 2.—This 23 year old white man of German descent was committed to the institution with a diagnosis of hebephrenic schizophrenia of a rather severe nature. The patient was consistently withdrawn socially and inactive physically. He was able to maintain his weight on only 80 per cent of the standard diet and, therefore, received 0.44 mg. of riboflavin per day. He was tall and flabbily muscled with fine skin and light complexion; his hair was brown, and his beard was auburn. He had chronic acne vulgaris of the face which changed little throughout the period of observation, either before, during or after riboflavin supplementation.

Early in January 1948, eight months after the inception of the deficient diet, the patient had a paronychial infection of the first toe of the left foot and shortly thereafter a similar lesion on the same toe of the right foot. During therapy with elevation and hot packs he became emotionally disturbed, combative and incontinent of urine and feces. Subsequently, the infection in the toes improved, but the patient continued to be disturbed, ate poorly and suffered from many delusions of a persecutory nature about his food. Occasional incontinence of urine and feces continued. During the third week in February, a scaling, erythematous lesion of the scrotum similar to that seen in the previous patient was first noted. This progressed rapidly to a raw, oozing, inflamed area, especially on the left, involving the inner aspect of the thigh. Some perianal inflammation and another raw area in the pilonidal region developed. The scrotum was elevated on a cloth sling, and continuous wet packs of isotonic sodium chloride solution were applied. Within 24 hours the acute maceration was relieved and the oozing of serum stopped. Subsequently, a pronounced erythema remained (fig. 1 *C*), and the skin over the anterior aspect of the scrotum became lichenified and violaceous. The adjacent thigh and pilonidal area healed slowly, but the scrotum remained inflamed and scaling. The patient continued to be disturbed and uncooperative.

About three weeks after the appearance of the scrotal lesion a small fissure with a honey-colored crust appeared at the right oral angle. There was no preceding herpes infection, and the patient's teeth were normal. Two days later a similar area of stomatitis appeared

on the left. These lesions did not involve the buccal mucous membrane. The lips were somewhat red and dry but did not reveal the typical fissuring and desquamation of cheilosis. Because of the severity of the scrotal lesion, which had persisted for almost a month, and the appearance of the angular stomatitis it was decided to supplement this subject's diet with 6 mg. of riboflavin per day, and this was started on March 10, 1948.

The response to therapy with riboflavin in this case was dramatic. Definite improvement in the scrotum was obvious by the third day, and within a week the scaling and most of the erythema were gone. The stomatitis also was entirely healed within one week. Subsequently, there was one episode of mild exacerbation of the scrotal erythema and scaling of short duration. Like the previous subject, slight erythema without scaling persisted for several months. The patient's disturbed behavior also rapidly returned to normal following supplementation. It was impossible to evaluate the role of the vitamin deficiency in his emotional disturbance.

CASE 3.—This 35 year old patient of Scotch descent was committed to the institution with a diagnosis of hebephrenic schizophrenia. He was fairly clear mentally but was socially withdrawn and physically inactive at all times. He was brown haired, also with auburn beard, and had light skin of fine texture. His build and stature were slight. He was cooperative at all times and never became emotionally disturbed. A mild erythema of the anterior aspect of the scrotum was first noted on Jan. 19, 1948—almost nine months after the inception of the riboflavin-deficient diet. The lesion soon progressed to a severe erythema with superficial scaling. As in the other two cases, the medial commissure was not involved (fig. 1 *D*). The patient did not complain of pruritus. The erythema and scaling persisted with only mild remissions until it was decided to supplement the subject's diet with 6 mg. of riboflavin 40 days after the onset of the dermatitis. Again the response to riboflavin was quite dramatic. Within six days, the scaling and dryness had entirely disappeared and the erythema had diminished. There was no recurrence of the inflamed and scaling lesion, but, as in the two previous cases, there was a residual mild erythema which persisted for several months. This patient at no time showed any other physical or mental signs of vitamin deficiency.

COMMENT

The preceding observations confirm the report of Sebrell and Butler[1] (1938) that signs of riboflavin deficiency may be observed at a dietary level of 0.5 mg. per day of riboflavin and support the view that they may develop in pure ariboflavinosis. In other respects our studies raise more questions than they answer. Are there any pathognomonic lesions of riboflavin deficiency? The widespread occurrence of angular stomatitis, scrotal dermatitis, vascularization of the cornea and glossitis in cases in which lack of riboflavin is clearly not the etiological factor indicate that there are not. One can merely imply that certain dermatological abnormalities have a predilection for persons with hyporiboflavinosis.

Review of our own findings and consideration of the reports of others have suggested a somewhat different concept of the role of low riboflavin ingestion in the pathogenesis of clinical abnormalities. That riboflavin is necessary for growth is generally agreed. Any local trauma to the dermal layer must be replaced by new growth. Will not the signs of deficiency, then, be partially dependent on the need for riboflavin for this local tissue replacement? If this is so, then the location of disorders of the dermal layer will depend on the presence of local irritations, infections and other traumas. Often the precipitating factor or the traumatic agent is not apparent, but in other instances it is. Note the angular stomatitis after herpes simplex, the nasal fissure after severe coryza and the widespread scrotal erythema of little consequence which becomes a lesion of moderate to considerable severity in the deficient subjects.

Consider the rats used in the present experiments. The control animals had occasional sores which came and went, but the sores which appeared in the deficient animals persisted. This was true for all wounds—those which were made experimentally and those which appeared for unknown reasons.

The conflict over vascularization of the cornea might readily be resolved on a similar basis. Thus, in aviators[19] subject to severe glare and eyestrain and deficient in riboflavin, proliferation of the limbic plexus could develop as a process of repair for small corneal lesions which had not healed in the normal manner.[33] The protected environment of our subjects would probably exclude any such injury.

Further evidence for this thesis was the early development of lesions in the subjects of this experiment who had red hair, auburn beards and fine skin. The three subjects whose histories were presented and the one subject reported on by Horwitt and his associates[22] as having displayed a definite angular stomatitis after a year on a diet providing 0.75 mg. of riboflavin per day all fall within this category. The sensitivity of the skin of such persons is well known.

The "yellow enzyme" is necessary in such a large number of cellular reactions (Sumner and Somers,[35] 1943) that it is surprising that abnormalities beneath the dermal layer were absent or minimal. The inability to find any changes in the metabolites in the body fluids may be because the cell, once matured, requires only a minimum amount of riboflavin. However, the rate of replacement of such cells with others may be dependent on a more abundant supply of riboflavin, obtainable either from the diet or through the breakdown of less vital tissue.

Regardless of the theoretical implications just discussed, it is well to note that the urinary excretion of riboflavin correlated well with the amounts ingested. About 25 per cent of the amount of riboflavin in a diet containing 1.6 mg. per day is excreted. Since the 24 hour excretion drops rapidly to approximately 10 per cent when the intake of riboflavin is lowered to 1.1 mg. per day and remains at 10 per cent for lower levels of intake, it can be suggested that the basal requirement for an adult male is between 1.1 and 1.6 mg. per day.[3] Emergency requirements during illness and for repair of tissue would necessarily be greater.

SUMMARY

The effects of diets restricted in riboflavin but otherwise adequate were observed in 15 male subjects. Fourteen other subjects were observed simultaneously as controls. Depletion with respect to riboflavin with a diet containing 0.55 mg. of riboflavin in 2,200 calories was maintained for nine to 17 months, during which period angular stomatitis, seborrheic dermatitis and scrotal skin lesions were observed.

Simultaneous experiments in which the same diet was fed to rats confirmed the inadequacy of the diet. In these animals retardation of wound healing was conspicuous.

Studies of the excretion of riboflavin in the urine suggest that the riboflavin requirement of a resting adult male is between 1.1 and 1.6 mg. per day and that a reserve of riboflavin cannot be maintained on levels of intake below 1.1 mg.

35. Sumner, J. B., and Somers, G. F.: Chemistry and Methods of Enzymes, New York, Academic Press, Inc., 1943.

Since previous studies revealed few abnormalities when the intake of riboflavin was above 0.6 mg. per day, it may be concluded that allowances below this amount are insufficient to support normal tissue repair. The type of abnormality then encountered will be dependent on the trauma, irritation, infection or other injuries to which the tissues are subjected.

Changes in the blood levels of lactic and pyruvic acids were not obtained on diets low in riboflavin, as opposed to the pronounced changes in carbohydrate metabolism observed during thiamine deficiency.

The following persons made important contributions to this study: Mr. William T. Sullivan, Mr. Otto Lobstein, Mr. Paul Riggs, Miss Charlotte Kaplan, Mr. Sidney Silberberg, Mr. Lazarus Astrachan and Mr. Kurt Schmeer, of the laboratory staff; Dr. Phyllis Wittman, Miss Arlene Ringold, Mrs. Mary Brown, Miss Esther Rollins and Miss Thelma Johnson, the psychologists; Miss Gordon Sampson and Mrs. Mary Meyers, the dietitians; Mrs. Pearl Ratcliff, Mrs. Beulah Spencer and Mrs. Maythel Newell, the cooks; Mrs. Edna Newtson, the nursing assistant, and the many attendants who assisted with the subjects. Dr. I. Zapolsky joined the project during its final stage to assume the duties of Dr. O. W. Hills, who left to accept a fellowship at the Mayo Clinic.

Photographs by Mr. Paul Riggs, F.B.P.A.

INTERMITTENT BUNDLE BRANCH BLOCK OF LONG DURATION

Vagal Influence on Intraventricular Conduction

GORDON E. HEIN, M.D.
AND
PAUL J. SANAZARO, M.D.
SAN FRANCISCO

NONPERMANENT bundle branch block is a frequent electrocardiographic finding. Lewis [1] recorded it first, and the literature concerning it has been reviewed by Sabathié,[2] Rasario,[3] Yater [4] and Comeau and associates.[5] Numerous synonyms have been applied to this condition, each synonym indicating somewhat different circumstances of occurrence. The terms transient,[6] paroxysmal,[7] incomplete,[8] inconstant [9] and functional [10] have been applied to the brief episodes of impaired bundle branch conduction appearing in the course of tachycardia or auricular arrhythmias,[11] coronary occlusion or insufficiency,[12] congestive heart

Dr. Hein is Chief of Medical Service, Veterans Administration Hospital, and Clinical Professor of Medicine, University of California Medical School.

Dr. Sanazaro is Resident in Medicine, Veterans Administration Hospital.

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1. Lewis, T.: An Address on Certain Physical Signs of Myocardial Involvement, Brit. M. J. **1**:484, 1913.

2. Sabathié, L. G.; Gaspary, F. V., and Rojas, R. A.: Bloqueos intraventriculares inestables, Rev. argent. cardiol. **11**:297, 1944.

3. Rasario, G. M.: Sui blocchi di branca instabili, Cuore e circolaz. **24**:139, 1940.

4. Yater, W. M.: Pathogenesis of Bundle Branch Block: Review of the Literature; Report of 16 Cases with Necropsy and of 6 Cases with Detailed Histologic Study of the Conduction System, Arch. Int. Med. **32**:1 (July) 1938.

5. Comeau, W. J.; Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle Branch Block Associated with Heart Disease: Review and Analysis of Literature, with 13 New Cases and Notes upon Influence of Vagus, Am. Heart J. **15**:276, 1938.

6. (*a*) Kurtz, C. M.: Transient Complete Bundle Branch Block, Am. Heart J. **11**:212, 1936. (*b*) Morris, R. S., and McGuire, J.: Transient Complete Bundle Branch Block, Am. J. M. Sc. **184**:202, 1932.

7. Comeau and others.[5] Bohnengel, C.: Paroxysmal Bundle Branch Block Associated with Physiologic Changes in a Patient with Organic Heart Disease, Am. Heart J. **16**:587, 1938.

8. Stenström, N.: Contributions to the Knowledge of Incomplete Bundle Branch Block in Man, Acta med. scandinav. **57**:385, 1922.

9. Donath, F.: Über inkonstanten Schenkelblock und über die Wirkung von Corphyllamin auf das Herz, Ztschr. f. klin. Med. **132**:802, 1937.

10. Carr, F. B.: Functional Bundle Branch Block, New England J. Med. **209**:1101, 1933.

11. (*a*) Comeau and others.[5] (*b*) Eichert, H.: Transient Bundle Branch Block Associated with Tachycardia, Am. Heart J. **31**:511, 1946. (*c*) Gilbert, N. S.: Paroxysmal Nodal Tachycardia with Aberrant Ventricular Pattern, Am. Pract. **1**:279, 1950.

failure,[13] thyrotoxicosis,[14] pulmonary embolism,[15] infectious diseases,[16] uremia,[17] congenital heart disease,[18] transient hypertension[19] and quinidine or digitalis administration.[20] Infrequently there is no detectable cardiac disease.[21] When no cardiac disease exists, the block has been designated "functional bundle branch block," a term also applied to the Wolff-Parkinson-White syndrome.[22] For clarity, the discussion which follows excludes specifically the consideration of the last-named entity.

Intrinsic heart disease is present in the majority of patients with transient bundle branch block, most commonly arteriosclerotic coronary artery disease, left ventricular hypertrophy or rheumatic heart disease.

The terms intermittent,[20b] recurrent[23] or unstable[24] bundle branch block refer to conduction disturbances which spontaneously appear and disappear over long periods in no definite relation to cardiac disease or extracardiac factors. These disturbances are rare. Patients have been described in whom apparently stable

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12. Bousfield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysm, Lancet **2**:457, 1918. Master, A. M.; Dack, S., and Jaffe, H. L.: Bundle Branch and Intraventricular Block in Acute Coronary Occlusion, Am. Heart J. **16**:283, 1938.

13. Comeau and others.[5] Carr.[10] Willius, F. A., and Anderson, M. J.: Transient Recurrent, Complete Bundle Branch Block, Am. Heart J. **10**:248, 1934. Willius, F. A., and Keith, N. M.: Intermittent Incomplete Bundle Branch Block, ibid. **2**:255, 1927.

14. Hill, I. G. W.: Bundle Branch Block: A Clinical and Histological Study, Quart. J. Med. **23**:15, 1930. Lamb, A. E.: Bundle Branch Block in Hyperthyroidism, M. Times & Long Island M. J. **61**:234, 1933.

15. Durant, T. M.; Ginsburg, I. W., and Roesler, H.: Transient Bundle Branch Block and Other Electrocardiographic Changes in Pulmonary Embolism, Am. Heart J. **17**:423, 1939.

16. (*a*) Hubert, G.: Beobachtungen über einen Fall von ausheilendem rechtsseitigem Schenkelblock, Ztschr. Kreislaufforsch. **27**:449, 1935. (*b*) Langley, R. W.; Reed, J. C., and Utz, D. C.: Bundle Branch Block: A Review of 100 Cases, Am. Heart J. **33**:730, 1947. (*c*) Segers, M.; Lequime, J., and Denolin, H.: Rémission progressive d'un bloc de branche, Acta cardiol. **2**:64, 1947. (*d*) Stecher, R. M.: Electrocardiographic Changes in Diphtheria: II. Intraventricular Block, Am. Heart J. **4**:715, 1929.

17. Moore, N. S., and Stewart, H. J.: The Disappearance of Intraventricular Heart-Block Occurring in Uremia Following the Intravenous Injection of Hypertonic Glucose Solution, Am. Heart J. **5**:469, 1930.

18. Wood, F. C.; Jeffers, W. A., and Wolferth, C. C.: Follow-Up Study of 64 Patients with a Right Bundle Branch Conduction Defect, Am. Heart J. **10**:1056, 1935.

19. Suarez, R. M.: Bloqueo de rama transitorio, Bol. Asoc. méd. Puerto Rico **38**:375, 1946.

20. (*a*) Benchimol, A. B.: Bloqueio de ramo instável, Arq. clín. **1**:483, 1945. (*b*) Katz, L. N.: Electrocardiography: Including an Atlas of Electrocardiograms, Philadelphia, Lea & Febiger, 1941, pp. 141 and 519. (*c*) Viko, L. E.; Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidin Sulphate, Arch. Int. Med. **31**:345 (March) 1923.

21. Langley and others.[16b] Fisch, C.: Bundle Branch Block of the Broad S Type: Report of Eleven Cases Without Any Evidence of Heart Disease, with One Instance Showing Partial and Transient Block, J. Indiana M. A. **40**:1128, 1947. Graybiel, A.; McFarland, R. A.; Gates, D., and Webster, F. A.: Analysis of Electrocardiograms Obtained from 1,000 Young Healthy Aviators, Am. Heart J. **27**:524, 1944.

22. Wolff, L.; Parkinson, J., and White, P. D.: Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, Am. Heart J. **5**:685, 1930.

23. Bishop, L. F., Jr.: Transient, Recurrent Complete Left Bundle Branch Block: Report of a Case, Am. Heart J. **15**:354, 1938.

24. (*a*) Benchimol.[20a] (*b*) Bagnaresi, G.: Il blocco di branca instabile, Cuore e circolaz. **18**:65, 1934. (*c*) Vesell, H.: Critical Rates in Ventricular Conduction: Unstable Bundle Branch Block, Am. J. M. Sc. **202**:198, 1941.

bundle branch block spontaneously disappeared after durations of ten months to four years.[25] Sabathié [2] observed a patient over a four year period in whom there persisted irregular alternation of normal intraventricular conduction with bundle branch block (partial bundle branch block). Bishop [23] recorded the persistence for three years of intermittent bundle branch block, after which time it became permanent. The case we are reporting is unique in that left bundle branch block was known to be present intermittently at least four years. Further, the variable state of conduction was alterable by physiological or pharmacologic maneuvers affecting vagal tone: In the presence of bundle branch block direct or reflex vagal stimulation resulted in slowing of the cardiac rate and appearance of normal intraventricular conduction.

REPORT OF A CASE

First Admission.—D. R. B., a 55 year old former painter, was admitted to the hospital on Sept. 28, 1946. According to the past history, he was first found to have hypertension in 1934. He enjoyed perfect health until January 1942, when he had an episode of painless nocturnal dyspnea. His physician made the diagnosis of "myocardial infarction" and ordered rest in bed for three months. Three weeks after the initial episode, sharp stabbing pains appeared below the left nipple, unrelated to exertion and unrelieved by administration of nitrites. He entered a hospital in March 1942 because of persistence of the pain and its recent radiation to the left shoulder. Results of blood studies and an electrocardiogram were normal. The patient was discharged after five days. He was rehospitalized in April 1942 for the same complaints. An electrocardiogram was interpreted as showing "an abnormal record of no characteristic pattern." The blood pressure at this time was 170/110. There was no clinical evidence of myocardial infarction or congestive failure. His precordial pains were relieved by treatment with erythrityl (erythrol®) tetranitrate tablets. He was discharged.

In September 1943 the sharp pains in the left anterior portion of the chest with radiation into his shoulder and upper arm reappeared intermittently, not definitely related to either rest or exercise but somewhat more frequently precipitated by the use of his left arm. He was confined to a veterans' rest home for 14 months. During this time he became free of all pain.

In November 1945 the pain in the left precordium reappeared with variable severity and was usually relieved by treatment with glyceryl trinitrate. At this time his blood pressure was 160/110. There was a persistent tachycardia of 100 with ticktack rhythm. An electrocardiogram was said to show left bundle branch block. Two tracings taken shortly afterward displayed normal intraventricular conduction.

He entered this hospital five days after the onset of burning, nonradiating pain in the anterior part of the chest on the left. The pain increased in severity and was accompanied with exertional dyspnea. The patient now stated that he had had nocturnal dyspnea for a number of years.

Physical Examination: The temperature was 99 F., the pulse rate 136 and regular, the blood pressure 152/86 and the respirations 24. The patient appeared to be middle-aged; he was lying quietly in bed in no apparent distress. Ocular examination showed the fundal arteries to be reduced in caliber. The mouth was edentulous. Examination of the chest revealed moderate emphysema. The lungs were clear to auscultation. The heart had an undefined area of dulness, with rapid regular rhythm, sounds of fair quality and embryocardia. The aortic second sound was louder than the pulmonary second sound. Abdominal and neurological examinations disclosed essentially normal conditions. The extremities displayed no edema.

Course: Burning pains in the left side of the chest continued throughout the period of hospitalization. The patient remained afebrile. The white blood cell count ranged from 6,400 to 7,700, with normal differential counts. Sedimentation rates varied from 32 to 42 mm. (Westergren). Numerous electrocardiograms were taken, in which the picture varied from that of

25. Comeau and others.[5] Kurtz.[6a] Bates, W. H.: Bundle Branch Block with Spontaneous Remission After 18 Months, Arizona Med. **6**:21, 1949. Delachaux, A.: Blocs de Wilson instables, Cardiologia **15**:47, 1949. Kalett, J.: Bundle Branch Block with Spontaneous Remission After 4 Years: Report of Case, Am. Heart J. **29**:120, 1945.

normal intraventricular conduction to that of left bundle branch block (fig. 1). On the tracings showing normal conduction, an inverted T wave in lead CF_4 was noted, which was thought to be consistent with an old anterior myocardial infarction. It was felt that no active myocardial disease was present and that a cardiac neurosis was responsible for the precordial pains. Acromioclavicular osteoarthritis was diagnosed as the cause of the shoulder pain. The episodes of nocturnal dyspnea were attributed to bronchial asthma rather than to left ventricular failure. He was discharged somewhat improved after 109 days.

Second Admission.—The patient reentered the hospital March 12, 1947 because of recurrence of severe burning pain in the left anterior portion of the chest six days before.

On admission, the vital signs were a temperature of 97.8 F., a pulse rate of 90, a respiration rate of 16 and a blood pressure reading of 192/104. Results of physical examination were the same as on the previous admission. Urinalysis showed a faint reaction for albumin. The white

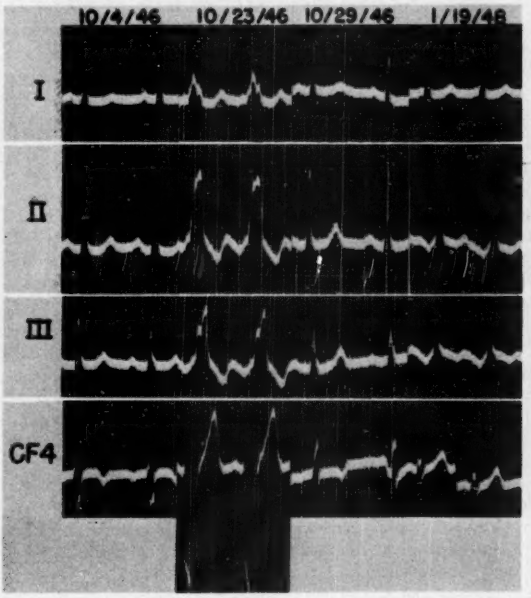

Fig. 1.—Left bundle branch block is present, with a nodal rhythm at a rate of 120, on Oct. 23, 1946, while normal intraventricular conduction occurs with a nodal rate of 130 on Jan. 19, 1948.

blood cell count was 8,800. The sedimentation rate was 15 mm. (Westergren). The patient's symptoms disappeared overnight without treatment, and he was discharged within five days.

Third Admission.—The patient was hospitalized Oct. 17, 1947 with a complaint of steady, burning pain in the anterior portion of the chest on the left for the preceding two weeks. This was not influenced by exercise, posture or food intake and was not associated with cough or dyspnea.

Physical Examination: The temperature was 99 F. The pulse rate was 99, and the blood pressure was 170/70. The eyes showed pronounced arcus senilis. The fundal arteries were markedly narrowed. There was limited expansion of the chest. The lungs were clear to percussion and auscultation. Breath sounds were distant. There was an apical impulse in the sixth interspace at the midclavicular line. Tones were muffled, and a ticktack rhythm was present. No murmurs were audible. The brachial arteries were thickened and tortuous. The edge of the liver was at the costal margin and was smooth and nontender. A chest roentgeno-

gram revealed normal outlines of the heart and great vessels. On laboratory studies the results of urinalysis were normal. The white blood cell count was 7,300, and the sedimentation rate 16 mm. (Westergren).

Course: The pain in the chest gradually disappeared with rest in bed. No therapy was given. He was discharged on the eighth day.

Fourth Admission.—The patient was readmitted Nov. 1, 1947 because of recurrence of left-sided chest pain which was constant, sharp and not relieved by treatment with glyceryl trinitrate. Results of physical examination and laboratory studies were similar to those of his previous entry.

Roentgenograms of the cervical and thoracic portions of the spine showed moderate degenerative fringing. Gallbladder visualization was normal. Electrocardiograms revealed normal intraventricular conduction, even during an episode of auricular (or nodal) tachycardia with a ventricular rate of 130 (fig. 1). Except for a transient episode of mild bronchopneumonia, which readily responded to penicillin therapy, the patient remained afebrile. Many mild attacks of difficult respiration were noted, and the attending allergist felt that bronchial asthma of the intrinsic variety was responsible for these episodes, as well as for the occasional nocturnal breathlessness. Administration of ephedrine, ⅛ grain (25 mg.), with amobarbital (amytal®), ¼ grain (50 mg.), relieved these symptoms.

The chest pains responded indifferently to use of nitrites and aminophylline. Phenobarbital administration afforded the greatest relief. The patient was discharged somewhat improved after 103 days' hospitalization.

Fifth Admission.—The patient was again admitted Nov. 17, 1948 with complaints of pain in the left side of the chest and shortness of breath of three weeks' duration. Earlier this year he had had three months' hospitalization elsewhere for similar complaints. Three weeks prior to this entry gradual onset of shortness of breath was noted, along with attacks of nocturnal dyspnea not relieved by use of ephedrine. Three days prior to entry constant, severe, nonradiating precordial pain developed.

Physical Examination: The temperature was 98.6 F. The pulse rate was 114. Respirations numbered 20. The blood pressure was 166/100. Positive findings included the following: Moderate emphysema with expiratory wheezes and scattered rhonchi was present throughout both lung fields. The heart was not enlarged, and no murmurs were audible. A gallop rhythm due to split mitral first sound was heard. The liver was palpable in the epigastrium but was not tender. Laboratory examination revealed sedimentation rates of 21 to 25 mm. (Westergren), 4,630,000 red blood cells, 7,900 to 8,450 white blood cells and 14.5 Gm. of hemoglobin per 100 cc. Urinalysis gave normal results. Cholesterol measured 300 mg. per 100 cc. Carbon dioxide was 26.6 and chlorides 86.6 milliequivalents per liter. Serologic tests for syphilis had negative results. The prothrombin time was 100 per cent of normal. The chest roentgenogram was normal. Electrocardiograms showed left bundle branch block, which disappeared with right carotid sinus pressure (fig. 2).

Course: The shortness of breath and moderately severe pain in the left side of the chest continued for three weeks, unabated by use of papaverine or aminophylline but partially relieved by glyceryl trinitrate administration. Digitalis was then given, with slow but steady improvement in symptoms for several weeks. However, the pain in the left side of the chest recurred. With the postulate that the persistent tachycardia was an important factor in his pain, neostigmine (prostigmin®) methylsulfate, 1 mg., was given hypodermically every four hours. The cardiac rate was reduced; the bundle branch block disappeared, and the precordial aching was relieved. However, as the asthmatic symptoms were aggravated by the medication, it was discontinued. A stellate ganglion block was performed on March 9, 1949 which gave immediate, complete relief to the patient of all pain in the chest for 10 days. He was discharged April 16, 1949.

Sixth Admission.—The patient was rehospitalized Nov. 30, 1949 because of severe cough and dyspnea of eight days' duration.

Physical Examination: The temperature was 98.6 F. The pulse rate was 120, with 24 respirations. The blood pressure was 150/90. The patient appeared acutely ill, dyspneic and orthopneic. There was frequent cough productive of purulent sputum. The eyes showed silver

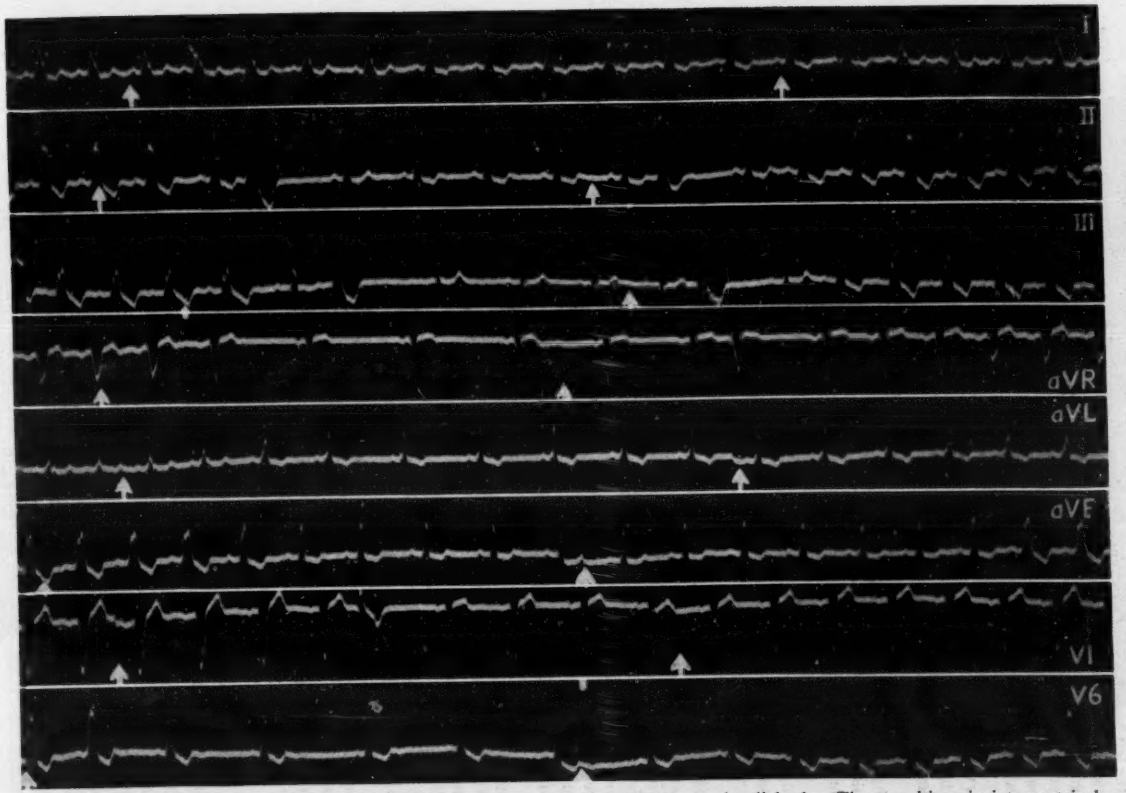

Fig. 2 (Dec. 2, 1948).—Right carotid sinus pressure was applied between arrows in all leads. The transitions in intraventricular conduction occur gradually in almost all instances.

streaking of the fundal arteries with increased tortuosity. The chest was emphysematous. The expiratory phase of respiration was prolonged, and breath sounds were diminished over the left hemithorax. Coarse tubular rales and rhonchi were present throughout. The size of the heart was not defined by percussion. The pulse rate was 120 and the rhythm regular. Marked gallop rhythm was present. No murmurs were audible. The aortic second sound equaled the pulmonary second sound in intensity. No definite liver edge was felt. The extremities displayed no dependent edema, and the pedal pulses were weak. Laboratory examination showed 7,400 white blood cells, with a normal differential count. The red blood cells numbered 4,800,000. The hemoglobin content was 13.5 Gm. per 100 cc. The corrected sedimentation rate was 8 mm. (Westergren). Urinalysis gave normal results. The sputum was loaded with gram-positive diplococci. Diplococcus pneumoniae was grown on culture. The chest roentgenogram showed an essentially normal condition.

Course: The patient was treated with penicillin aerosol and isopropylarterenol (isuprel®) hydrochloride. Prompt improvement occurred. Although evidence of his acute bronchitis subsided, scattered expiratory wheezes and some cough persisted. This was attributed to his bronchial asthma. The patient was discharged Dec. 7, 1949.

Seventh Admission.—The patient was again admitted Jan. 18, 1950 because of persistent aching pain in the right shoulder and arm of 18 days' duration. Self medication with anacin® (a mixture of acetophenetidin, acetylsalicylic acid, caffeine and quinine sulfate) and acetylsalicylic acid brought no relief.

Physical Examination: The temperature was 98.6 F., the pulse rate 112, the respiration rate 18 and the blood pressure 155/110. The significant findings were bronchial wheezing audible on deep respiration and pronounced diastolic gallop rhythm audible at the cardiac apex. The right hand showed decreased sweating. Laboratory examination revealed the serologic reactions for syphilis to be negative. Urinalysis gave normal results. Red blood cells numbered 4,700,000 and white blood cells 5,700. The hemoglobin content was 13 Gm. per 100 cc. Roentgenograms revealed mild osteoarthritis of the acromioclavicular joint and moderate osteoarthritis of many of the terminal interphalangeal joints. The cervical portion of the spine showed marked fringing of the midcervical joints on their ventral aspects.

Course: On admission, a tentative diagnosis of shoulder-hand syndrome was made. A right stellate ganglion block was induced with administration of procaine hydrochloride solution. Simultaneous with the appearance of Horner's syndrome on the right, there was complete disappearance of all pain. This persisted approximately 1½ hours. Pain recurred with the disappearance of Horner's syndrome. Subsequently, it was felt that the pain was more typical of segmental neuralgia. Physical therapy was given, with slow, gradual improvement. The patient was discharged Feb. 16, 1950.

The final diagnoses at this time were (1) arteriosclerotic heart disease, with (*a*) left intraventricular conduction defect (intermittent), (*b*) persistent tachycardia, (*c*) gallop rhythm and history of myocardial infarction; (2) bronchial asthma; (3) emphysema, and (4) osteoarthritis of the cervical and thoracic portions of the spine.

OBSERVATIONS

It was noted that four years after the initial observations, the patient continued to exhibit marked sensitivity to carotid sinus stimulation, as shown by cardiac slowing and abolition of the left bundle branch block pattern on the electrocardiogram (fig. 3). Various maneuvers were then tested for their effect on this mechanism. In the presence of normal intraventricular conduction mild exercise which raised the cardiac rate only slightly resulted in reappearance of the block (fig. 4). Neostigmine methylsulfate given subcutaneously reduced the cardiac rate transiently, and the bundle branch block disappeared during this period (fig. 5). With the patient under the influence of neostigmine methylsulfate, administration of atropine sulfate overcame the parasympathomimetic effect and raised the cardiac rate sufficiently to induce bundle branch block (fig. 6). In the presence of bundle branch block phenylephrine (neo-synephrine®) hydrochloride given intravenously raised

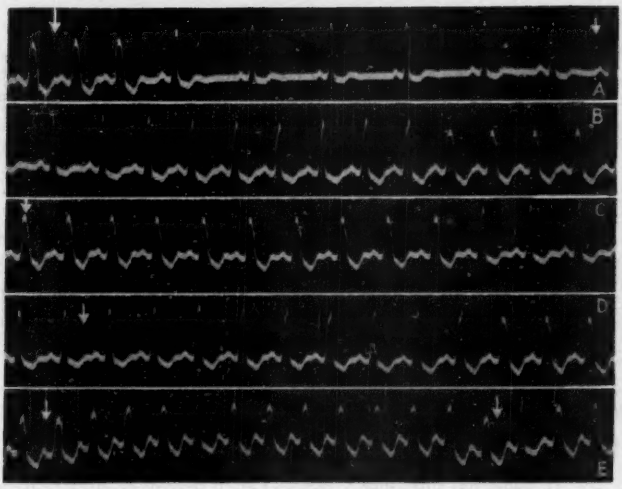

Fig. 3 (lead II, June 1, 1950).—*A* and *B* are continuous, with right carotid sinus pressure applied between arrows. *C* and *D* are continuous, showing effect of left carotid sinus stimulation. *E* illustrates failure of right carotid sinus pressure to alter either rate or intraventricular conduction in the presence of atropinization.

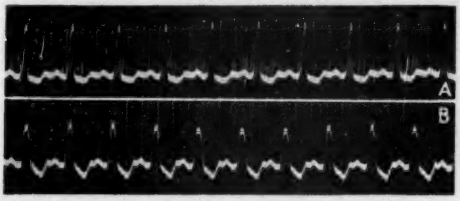

Fig. 4 (lead II, June 2, 1950).—*A*, patient resting. Ventricular rate, 100; QRS interval, 0.10 second. *B*, immediately after three sit-ups. Ventricular rate, 110; QRS interval, 0.14 second.

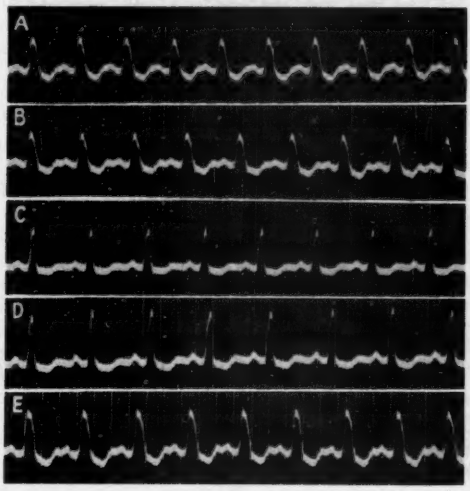

Fig. 5 (lead II, May 30, 1950).—*A*, neostigmine methylsulfate, 1 mg., was given subcutaneously at beginning of record. Rate, 115; QRS interval, 0.15 second. *B*, eight minutes later. Rate, 105; QRS interval, 0.14 to 0.15 second. *C*, 12 minutes after injection. Rate, 93; QRS interval, 0.10 to 0.11 second. *D*, 27 minutes after injection. Rate, 90; QRS interval, 0.10 to 0.11 second. *E*, 35 minutes after injection. Rate, 95; QRS interval, 0.15 to 0.16 second.

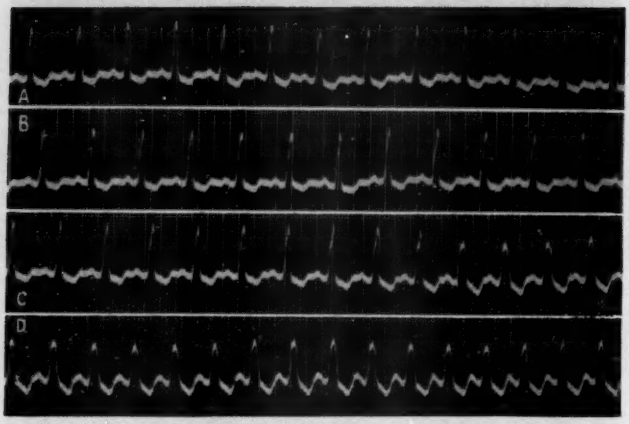

Fig. 6 (lead II, continuous strip, June 1, 1950).—Patient received neostigmine methylsulfate, 1 mg., subcutaneously 23 minutes prior to record. Atropine sulfate, 1 mg., given intravenously at beginning of *A*. Initial rate, 97; QRS interval, 0.10 second. In strip *C*, transition to complete bundle branch block occurs at rate of 108. In *D*, ventricular rate is 120 and QRS interval varies from 0.12 to 0.15 second.

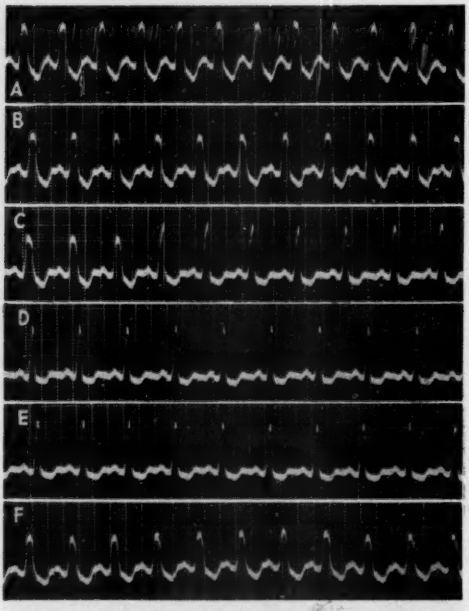

Fig. 7 (lead II, June 1, 1950).—Phenylephrine hydrochloride, 0.75 mg., was given intravenously at beginning of record. *A*, blood pressure, 142/85; ventricular rate, 130; QRS interval, 0.14 second. *B*, 40 seconds later. Blood pressure, 180/115; rate, 110; QRS interval, 0.14 second. *C*, transition occurs 68 seconds after injection. Blood pressure, 185/110; rate, 105; QRS interval, 0.10 second. *D*, four minutes after injection. Blood pressure, 165/95; rate, 98; QRS interval 0.08 to 0.09 second. *E*, 12 minutes after injection. Blood pressure, 160/92; rate, 100; QRS interval, 0.09 to 0.10 second. *F*, 17 minutes after injection. Blood pressure, 154/88; rate, 110; QRS interval, 0.14 second.

the arterial blood pressure and induced reflex cardiac slowing; concomitant with this, normal intraventricular conduction appeared (fig. 7). In the absence of all drugs except the routine digitalis dosage, a resting electrocardiogram showed spontaneous variations in QRS durations (fig. 8).

COMMENT

Temporary abolition of transient bundle branch block by reflex vagal action during forced inspiration and breathholding was first observed by Wilson and Herrmann.[26] Subsequently, Stenström[27] described the effects of carotid sinus pressure, Bagnaresi[24b] of ocular pressure and acetylcholine and Eichert[11b] of neostigmine. Cardiac slowing preceded normalization of the ventricular complexes in all instances. The original hypothesis that the improvement in bundle branch conduction is secondary to the slowing rather than to a primary vagal effect has been generally accepted.[27] The underlying pathological state which permits such variation in conductivity has been assumed to be an inadequate blood supply or fibrosis of the bundles, and the physiological factor has been postulated as being "fatigue" due to accumulation of acid metabolites or simply a lengthened refractory

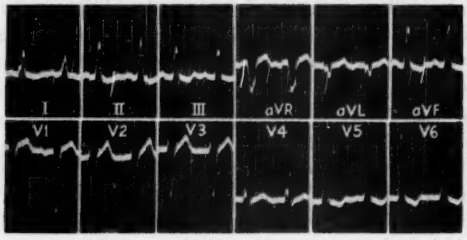

Fig. 8 (June 2, 1950).—Note spontaneous variation in QRS duration.

period.[28] In either instance cardiac slowing with prolonged diastolic resting phase permits conduction of each impulse normally. Oxygen,[29] glucose,[17] aminophylline[9] and amyl nitrite[30] have been used with temporary benefit, the presumed mechanism being improved nutrition or augmented blood supply of the affected bundle branch.

26. Wilson, F. N., and Herrmann, G. R.: Unusual Disturbances of the Mechanism of the Heart Beat, Arch. Int. Med. **31**:923 (June) 1923.

27. Stenström, N.: Further Experience in Incomplete Bundle Branch Block in Man, Acta med. scandinav. **67**:353, 1927.

28. (*a*) Yater.[4] (*b*) Stenström.[8] (*c*) Freundlich, J.: Über die Beeinflussung intraventrikulärer Leitungsstörung durch den Carotisdruck, Deutsches Arch. klin. Med. **168**:360, 1930. (*d*) Herrmann, G. R., and Ashman, R.: Partial Bundle Branch Block: A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle-Branch Block, Am. Heart J. **6**:375, 1931. (*e*) Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916. (*f*) Stenström, N.: An Experimental and Clinical Study of Incomplete Bundle Branch Block, Acta med. scandinav. **60**:552, 1924.

29. Baker, B. M.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block, Arch. Int. Med. **45**:814 (May) 1930.

30. von Metzingen, A.: Über einen Fall von functionellem Verzweigungsblock, Klin. Wchnschr. **13**:1158, 1934.

Pertinent experimental work by Scherf [31] in dog hearts indicated that, while normal bundle branch conduction occurred through partially sectioned branches at normal cardiac rates, delay or failure of transmission would result at higher rates, so that bundle branch block complexes resulted. Baschmakoff,[32] utilizing frog hearts, sectioned the ventricles so that only a narrow connecting strip remained. Whereas conduction was normal at slower rates, complete failure of conduction occurred when the cardiac rate was raised beyond a given level. He concluded that the blocked transmission was not due to a lengthened refractory period of the conducting tissues, but that each blocked impulse induced refractoriness in separate groups of fibers. The continued presence of refractoriness in a large number of the conduction fibers during tachycardia could thus block conduction.

Wilson and Herrmann,[33] Stenström [34] and Herrmann and Ashman [28d] have demonstrated that complete blockage of conduction in one bundle branch is not necessary for bundle branch complexes to appear. The latter may result from partial lesions of a bundle branch when the conduction time through this branch is greater than that through the opposite bundle branch and septum combined. If the conduction time is shorter, normal complexes appear. A delay of only 0.04 to 0.05 second in one branch has been thought sufficient to cause ventricular complexes indistinguishable from those resulting from complete blockage.[27] It is, therefore, possible for minor effects from nervous, humoral or vascular changes to influence ventricular complexes if there preexists a slight impairment of conductivity because of underlying cardiac disease.

The foregoing considerations can readily be applied to instances of transient bundle branch block which occur in the course of some serious cardiac disorder. The validity of these considerations is questionable in reference to chronic intermittent bundle branch block, as in the case we are describing. While undoubted coronary artery disease was present, there was no clinical correlation between the bundle branch block and the occurrence of demonstrable alterations in coronary circulation. Vesell [24c] has emphasized the concept of a "critical rate," above which impaired intraventricular conduction appears. However, in the case we have described there was no fixed correlation of ventricular rate with the presence of bundle branch block.

The repeated observation that vagal influences abolished the bundle branch block led to a consideration of the known vagal effects on intraventricular conduction.

Although Rothberger [35] in an extensive review concluded that the vagus exerts no effect on the cardiac conduction system distal to the auriculoventricular node, a number of observations indicate that vagal action may occasionally impair intraventricular or bundle branch conduction.

31. Scherf, D.: Reizleitungsstörungen im Schenkel, Klin. Wchnschr. **4**:2207, 1925.

32. Baschmakoff, W. I.: Die Bedingungen eines vollständigen funktionellen Herzblocks, Arch. ges. Physiol. **224**:167, 1930.

33. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920.

34. Stenström.[8] Stenström.[28f]

35. Rothberger, C. J.: Normale und pathologische Physiologie der Rhythmik und Koordination des Herzens, Ergebn. Physiol. **32**:472, 1931.

Eppinger and Rothberger [36] induced abnormal ventricular complexes in a dog's heart by incompletely sectioning the left bundle branch. Following vagal stimulation, complete bundle branch block appeared. However, focal hemorrhage at the incisional area may have contributed to this occurrence. Schliephake [37] demonstrated that vagal stimulation significantly altered the time relationships of the right and left ventricular contractions in dogs. Although vagal fibers have never been demonstrated in the septum and ventricular muscle, significant increases of *Vagusstoff* appear in the ventricular muscle following vagal stimulation.[38] Eckey,[39] however, in an extensive review, felt that the vagus exerted a negative chronotropic effect on intraventricular conduction by direct action rather than by any humoral mechanism.

Ritchie [40] first noted in human beings that carotid sinus stimulation at times leads to QRS prolongation. Wilson [41] and von Hoesslin [42] published the earliest tracings showing transition from normal conduction to the picture of bundle branch block during either carotid sinus stimulation or forced inspiration. Daniélopolu and Danulescu,[43] after administration of epinephrine or atropine (during the parasympathomimetic phase), recorded the development of bundle branch complexes on carotid sinus or ocular pressure. This maneuver was proposed as a provocative test for disclosing minimal lesions of the bundle branch system. The added inhibition was postulated to be sufficient to induce bundle branch block in the presence of already existing impairment of conduction, thus enabling electrocardiographic diagnosis of an otherwise undiscoverable lesion.

Kisch and Grishman,[44] Purks,[45] Comeau and co-authors,[5] Sigler,[46] Daniélopolu and associates [47] and Starr [48] have also published tracings demonstrating impairment

36. Eppinger, H., and Rothberger, J.: Über die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. klin. Med. **70**:1, 1910.

37. Schliephake, E.: Ein Beitrag zur Kenntnis der Vaguswirkung auf die Erregungsleitung im Säugetierherzen, Ztschr. Biol. **82**:107, 1924.

38. Engelhart, E.: Über humorale Übertragbarkeit der Herznervenwirkung: Die Vagusstoffverteilung auf Vorhof und Kammer bei Frosch und Säuger, Arch. ges. Physiol. **225**:721, 1930. Engelhart, E., and Loewi, O.: Über die Vagusstoffzerstörung im Herzen, Arch. internat. pharmacodyn. **38**:287, 1930.

39. Eckey, P.: Untersuchungen über autonome Nervenwirkungen auf die Herzkammern des Menschen, Arch. Kreislaufforsch. **5**:1, 1939.

40. Ritchie, W. T.: The Action of the Vagus on the Human Heart, Quart. J. Med. **6**:47, 1912.

41. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008 (Dec.) 1915.

42. von Hoesslin, H.: Ein Fall von Überleitungsstörung, bedingt durch Vagusreiz, Zentralbl. inn. Med. **34**:905, 1913.

43. Daniélopolu, D., and Danulescu, V.: Lésions latentes des branches du faisceau auriculo-ventriculaire: Moyens de les déceler, Arch. mal. cœur **14**:529, 1921; Trouble de conductibilité dans les branches du faisceau auriculo-ventriculaire provoqué chez l'homme normal par l'excitation du vague, ibid. **15**:361, 1922.

44. Kisch, B., and Grishman, A.: Transient Intraventricular Conduction Defect, Exper. Med. & Surg. **2**:277, 1944.

45. Purks, W. K.: Further Evidence in Regard to Functional Bundle Branch Block, Ann. Int. Med. **12**:1105, 1939.

46. Sigler, L. H.: Electrocardiographic Observations on the Carotid Sinus Reflex, Am. Heart J. **9**:782, 1934.

(Footnotes continued on next page)

of bundle branch or intraventricular conduction as a result of reflex vagal stimulation or use of parasympathomimetic drugs. While it has been argued that such demonstrations are invalid because of concomitant changes in auricular and auriculoventricular conduction, the abnormal complexes could only with difficulty be interpreted as escape beats or ventricular extrasystoles in every instance.

Finally, Sabathié,[2] Vesell,[24c] Lind [49] and Holzmann [50] reported cases in which spontaneous increases in vagal tone resulted in the appearance of bundle branch block. Elevation of the cardiac rate abolished the block every time.

Rasario [3] alone has proposed that the vagus may actually speed intraventricular conduction by direct action independent of cardiac slowing. He cites a case report in which bundle branch block occurring during an episode of paroxysmal auricular tachycardia was abolished by carotid sinus stimulation while the tachycardia was unaffected.[51]

The weight of evidence indicates that vagal excitation occasionally exhibits a negative chronotropic effect on bundle branch or intraventricular conduction. It is, therefore, not reasonable to assume that vagal stimulation produces a positive inotropic effect in the instances in which transient or intermittent bundle branch block is abolished by this maneuver.

The existence of intermittent conduction defects for prolonged periods has led to the use of the term "functional," since the unfavorable prognosis attached to such lesions was not borne out. Such designation is not correct in view of the serious underlying heart disease which is usually present. Rather, it is probable that complete blockage of bundle branch conduction has not occurred. It might be presumed, therefore, that the intracardiac lesion is not so advanced as in permanent bundle branch block. It is this factor, rather than the conduction defect, that determines the prognosis.

SUMMARY

A case of long-standing intermittent bundle branch block is described, in which direct or indirect vagal stimulation at all times abolished the block, when present.

A review is presented of the clinical and experimental work relating to the presence of vagal action on intraventricular conduction.

Most data indicate that such vagal action, when demonstrable, is inhibitory in nature. Possible rare exceptions may occur.

Abolition of transient or intermittent bundle branch block following direct or reflex vagal stimulation must be considered entirely secondary to the concomitant cardiac slowing, rather than to any vagal action on the conduction system. The local physiological mechanisms responsible for this phenomenon are unknown.

47. Daniélopolu, D.; Aslan, A.; Maxim, M.; Proca, G. G., and Marcu, L.: Die amphotrope karotische Reflexprobe zur Prüfung der Erregbarkeit des vegetativen Nervensystems, Wien. Arch. inn. Med. **17**:381, 1929.

48. Starr, I., Jr.: Acetyl-β-Methylcholin: III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, with a Discussion of Its Action in Other Conditions, Am. J. M. Sc. **186**:330, 1933.

49. Lind, J.: Electrocardiographic Changes Due to Vagal Effect, Nord. med. **24**:2181, 1944.

50. Holzmann, M.: Seltene Abarten von unbeständigen Schenkelblock, Cardiologia **7**:113, 1943.

51. Francaviglia, A., cited by Rasario.[3]

DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID IN THE TREATMENT OF RHEUMATOID ARTHRITIS

DONALD S. LITTMAN, M.D.
ROBERT H. STOCKDALE, M.D.
AND
GEORGE R. WILLIAMSON, M.D.
ASPINWALL, PA.

THE REPORTED success of Lewin and Wassén [1] in the treatment of rheumatoid arthritis with desoxycorticosterone acetate (DCA) and ascorbic acid indicates the importance of adequate studies to evaluate this therapy on an objective basis. Practically all the subsequent reports,[2] which appeared in rapid succession after the original publication, were of a clinical nature with little objective evidence. In most of these reports the period of observation was much too short, considering the variability and chronicity of the disease.

The program of study in the present investigation included the following: (1) administration of a low sodium diet; (2) careful and frequent clinical evaluations; (3) substitution of placebos at varying intervals without the knowledge of the participating physicians; (4) daily record of body weight; (5) frequent blood pressure determinations; (6) roentgenograms of heart and lungs; (7) electrocardiograms; (8) complete blood counts; (9) total circulating eosinophil count before (control) and four hours after medication; (10) urinalyses; (11) determination of sedimentation rates; (12) estimation of blood nonprotein nitrogen levels; (13) determination of fasting blood sugar levels; (14) urinary chloride determinations; (15) estimation of 24 hour urinary 17-ketosteroid excretion; (16) determina-

From the Medical Service, Veterans Administration Hospital, Aspinwall, Pa., and the University of Pittsburgh School of Medicine.

Drs. Littman and Stockdale are residents in internal medicine, and Dr. Williamson is attending in internal medicine, Veterans Administration Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Lewin, E., and Wassén, E.: Effect of Combined Injections of Deoxycortone Acetate and Ascorbic Acid on Rheumatoid Arthritis, Lancet **2**:993 (Nov. 26) 1949.

2. Le Vay, D., and Loxton, G. E.: Deoxycortone Acetate and Ascorbic Acid in the Treatment of Rheumatoid Arthritis, Lancet **2**:1134-1135 (Dec. 17) 1949. Douthwaite, A. H.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, ibid. **2**:1244-1245 (Dec. 31) 1949. Mettier, S. R.; Gordan, G. S.; Rinehart, T. F.; Plumhof, C.; Ellenborn, M. J., and McBride, A.: The Effect of Desoxycorticosterone Acetate and Vitamin C on Patients with Rheumatoid Arthritis: A Preliminary and Condensed Report, Bull. Univ. California M. Center **1**:337 (Jan.) 1950. Le Vay, D., and Loxton, G. E.: Clinical Observations with Deoxycortone and Ascorbic Acid, Lancet **1**:209-211 (Feb. 4) 1950.

tion of serum chloride levels; (17) determination of basal metabolic rate. The above laboratory studies were made during the control period and were repeated frequently throughout the remainder of the investigation. No deviation from the normal was encountered in any of the patients observed.

Initially the drugs were administered according to the method of Lewin and Wassén,[1] 5 mg. of desoxycorticosterone acetate given intramuscularly followed within three minutes by 1,000 mg. of ascorbic acid given intravenously. Later, the drugs were combined and administered intramuscularly.

The illustrations accompanying the case reports are graphic representations of the clinical course during the period of study. Both desoxycorticosterone acetate and ascorbic acid were given intramuscularly during the period of biweekly injections. The degree of clinical improvement shown is subjective. The circulating eosinophil counts were done according to the method of Thorn.[3] The sedimentation rates were determined by Cutler's method.

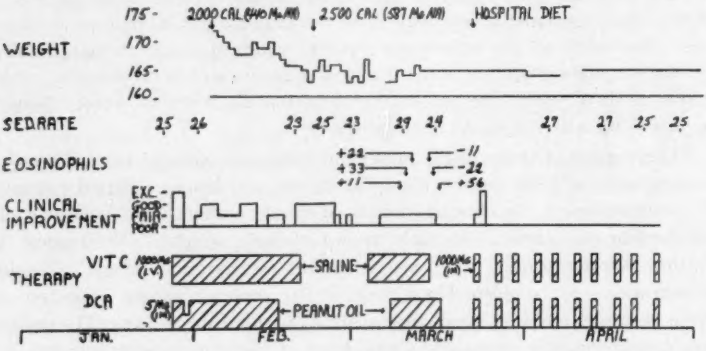

Fig. 1 (case 1).—Clinical course during administration of desoxycorticosterone acetate and ascorbic acid.

REPORT OF CASES

CASE 1.—W. K., a 59 year old white man, had chronic rheumatoid arthritis of five years' duration, with multiple joint involvement necessitating a bed and wheel chair existence. As can be seen in figure 1, the initial response to administration of desoxycorticosterone and ascorbic acid was excellent. Twenty minutes after the first injection his pain disappeared completely, and he was able to walk a distance of 50 feet (15 meters) in comparative comfort. There was an increase in motion of several joints, some of which showed a measurable improvement of 60 degrees. The patient remained free of pain for eight hours. Good response followed the second injection, but the improvement was not as great as on the previous day. Thereafter the response was variable, and subjective improvement was obtained with the use of placebos, as well as with the administration of desoxycorticosterone acetate and ascorbic acid. During the prolonged daily administration of desoxycorticosterone and ascorbic acid numerous silent venous thromboses occurred at the sites of ascorbic acid injection.

There can be no doubt that the initial subjective improvement was striking. Beyond this, however, the results were equally good during the administration of placebos.

3. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: The Response to the Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005-1009 (July 17) 1948.

CASE 2 (fig. 2).—E. K. was a 55 year old white man with chronic rheumatoid arthritis of 12 years' duration. He led a bed and wheel chair existence because of involvement of multiple joints. He had not walked unaided for over four months. Twenty minutes after the first injection of desoxycorticosterone acetate and ascorbic acid he stated that his pain was completely gone. He arose from his bed and was able to walk a distance of 20 feet (6 meters) unaided. He experienced a painless increase in motion of most of the affected joints. The beneficial response lasted 10 hours. The next day a similar result was obtained. After four days of treatment, during which time symptomatic improvement continued, the administration of a placebo failed to produce any response. When therapy was reinstituted, the response gradually diminished, although there was some improvement noted during the use of placebos. There was no response to twice weekly intramuscular injections of desoxycorticosterone acetate and ascorbic acid. Numerous silent venous thromboses made administration of ascorbic acid difficult. Definite improvement occurred with the initial use of desoxycorticosterone and ascorbic acid, but after this there was as much subjective improvement with the administration of placebos.

CASE 3.—R. W. was a 23 year old white man with chronic rheumatoid arthritis of six years' duration and rheumatoid spondylitis of six months' duration. He had painful swelling and limitation of motion of the right knee and painful limitation of motion of the right hip

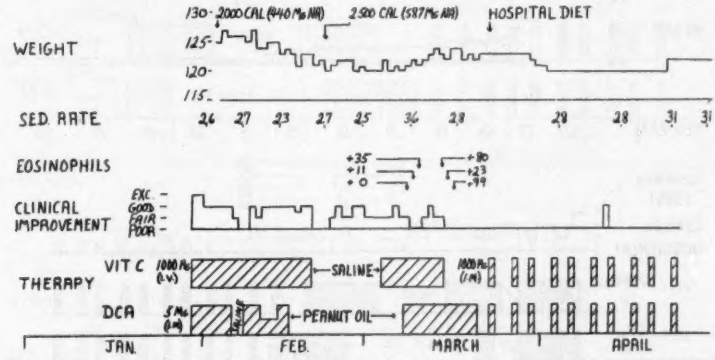

Fig. 2 (case 2).—Clinical course during administration of desoxycorticosterone acetate and ascorbic acid.

and lumbosacral portion of the spine. Roentgenograms revealed sclerosing changes in the sacroiliac joints and flattening of the lumbar curve. He was afebrile. He was given two injections of isotonic sodium chloride solution intramuscularly within four days with no response. He was then given combined intramuscular injections of 5 mg. of desoxycorticosterone acetate and 1,000 mg. of ascorbic acid twice weekly for a total of six doses. There was no subjective or objective improvement. He was subsequently given roentgen therapy to the spine with a good clinical response.

CASE 4.—H. M. was a 50 year old white man with chronic rheumatoid arthritis of 16 years' duration. He had involvement of multiple joints, with swelling of the right knee and both ankles, which resulted in a hobbling gait. He was afebrile; however, the sedimentation rate was elevated. After the intramuscular injection of isotonic sodium chloride solution there was no response. Eight hours after the first combined intramuscular injection of 5 mg. of desoxycorticosterone acetate and 500 mg. of ascorbic acid, he experienced decided diminution of pain in the joints and an increase in freedom of motion. He no longer hobbled, was able to get about the ward freely and could perform movements which had been impossible for over five years. This effect lasted only 48 hours and then could not be reproduced in spite of an increase in the dose of ascorbic acid to 1,000 mg. in combination with the desoxycorticosterone acetate. The initial improvement gradually disappeared, and all symptoms returned within one

week. The patient received a total of 18 twice weekly intramuscular injections of desoxycorticosterone with ascorbic acid. Urinary 17-ketosteroid determination revealed a control level of 10 mg. per 24 hours with a value of 11.3 mg. per 24 hours after the first injection of desoxycorticosterone with ascorbic acid. The sedimentation rate remained elevated.

CASE 5.—J. D. was a 28 year old white man with acute rheumatoid arthritis of six months' duration. He was febrile, with tachycardia and swelling, heat and tenderness of both knees and the right ankle. He was given 5 mg. of desoxycorticosterone acetate intramuscularly with 1,000 mg. of ascorbic acid intravenously daily for eight days. Next he received 5 mg. of desoxycorticosterone intramuscularly with isotonic sodium chloride solution intravenously daily for six days. After this, he received two combined intramuscular injections of 5 mg. of desoxycorticosterone acetate and 500 mg. of ascorbic acid four days apart. At no time was there any subjective or objective improvement. Fever and tachycardia persisted, and the right knee became even more swollen and painful. Urinary 17-ketosteroid excretion revealed a control level of 20.1 mg. per 24 hours, with a value of 15.5 mg. per 24 hours after the last injection of desoxycorticosterone and ascorbic acid. Later he was given pituitary adrenocorticotropic hormone (ACTH) with good clinical response.

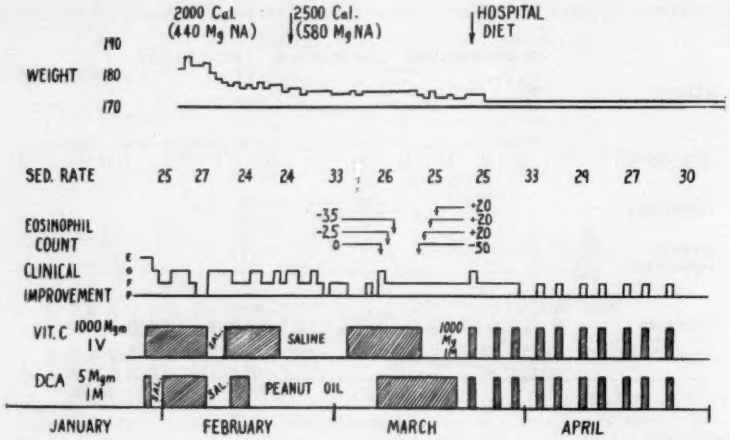

Fig. 3 (case 7).—Clinical course during administration of desoxycorticosterone acetate and ascorbic acid.

CASE 6.—A. L. was a 55 year old white man with chronic rheumatoid arthritis of five years' duration and osteoarthritis of the lumbar part of the spine. He had involvement of multiple joints, with swelling of both ankles, but was afebrile. Prior to treatment he complained that stiffness and pain prevented him from becoming ambulatory. There was no response to placebo injections. He was given a combined intramuscular injection of 5 mg. of desoxycorticosterone acetate and 500 mg. of ascorbic acid. This was followed in five hours by diminution of pain in the ankles. He was then given combined intramuscular injections of 5 mg. of desoxycorticosterone acetate with 1,000 mg. of ascorbic acid twice weekly for a total of 18 injections. During the second week he noted less pain, had a feeling of well-being and became ambulatory. The improvement was entirely subjective and was maintained by injections of isotonic sodium chloride solution. The sedimentation rate remained elevated throughout the period of observation. Urinary 17-ketosteroid excretion revealed a control value of 8.3 mg. per 24 hours, with an excretion of 7.1 mg. per 24 hours after the first combined injection of desoxycorticosterone and ascorbic acid.

CASE 7.—P. B. was a 26 year old white man with rheumatoid arthritis of two years' duration. There was involvement of almost all the peripheral joints, with severe deformities and loss of

function. As can be seen in figure 3, an excellent subjective improvement was noted the first two days. The patient walked 20 to 30 feet (6 to 9 meters) unaided after the first two injections, whereas prior to this he was able to walk only two or three steps without aid because of pain. Thereafter, the subjective improvement was fair to good with administration of the combination of desoxycorticosterone and ascorbic acid or with the use of placebos. The response to biweekly

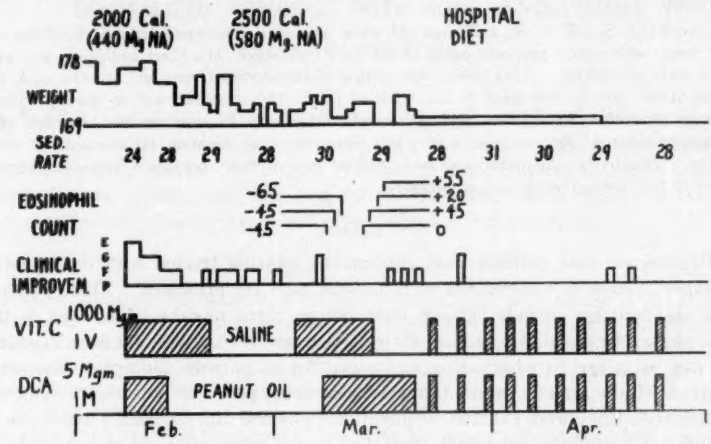

Fig. 4 (case 8).—Clinical course during administration of desoxycorticosterone acetate and ascorbic acid.

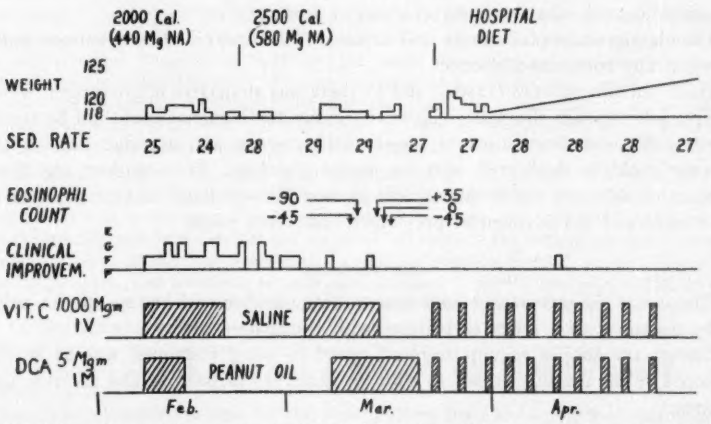

Fig. 5 (case 9).—Clinical course during administration of desoxycorticosterone acetate and ascorbic acid.

intramuscular injections of desoxycorticosterone and ascorbic acid was fair. Absolutely no objective improvement was seen at any time.

Case 8.—H. C. K. was a 56 year old white man suffering from a recent exacerbation of chronic rheumatoid arthritis of eight years' duration. Many of the peripheral joints were acutely involved. Figure 4 shows the initial excellent and good subjective responses during the first

five days of treatment. Prior to treatment he had been strictly a bed patient, but after the first few injections he was able to walk approximately 50 feet. Fair relief of pain was experienced while he received peanut oil and saline solution. There was no response to ascorbic acid given alone, and at times fair improvement was noted with desoxycorticosterone administered alone. Mild sporadic relief was noted with biweekly intramuscular injections. Objectively, there was progression of the disease in the affected joints, as well as involvement of joints previously unaffected.

CASE 9 (fig. 5).—F. S. R., a 22 year old white man, had rheumatoid arthritis involving the right knee, both ankles and both heels of one year's duration. His chief complaint was pain in the heels on walking. After initial injections of desoxycorticosterone and ascorbic acid, the patient stated that he had good to fair relief of pain. This response was as readily elicited when he received saline solution and peanut oil. Practically no response was observed with desoxycorticosterone and ascorbic acid given alone or in combination intramuscularly twice weekly. Objectively, the patient showed gradual improvement consistent with the natural course of this disease, unaffected by treatment.

SUMMARY

Reports on nine patients with rheumatoid arthritis treated with desoxycorticosterone acetate in combination with ascorbic acid are presented. These patients were observed for periods varying from one to three months. One was in the acute phase; the remainder had had their disease one to 16 years. All were disabled, and five led a bed to wheel chair existence. In all patients multiple joints were involved. Daily, and in most instances twice daily, progress notes were made on all patients. They were checked frequently for physical and laboratory evidences of toxicity. The study was carefully controlled by the substitution for varied intervals of placebo medication without the knowledge of the participating physicians.

At no time, even during the daily administration of desoxycorticosterone acetate and ascorbic acid, was there any evidence of toxicity.

Circulating eosinophil counts and urinary 17-ketosteroid determinations failed to reveal any cortisone-like effect.

In all but two patients (cases 3 and 5) there was subjective improvement, which in three patients was dramatic. However, either the response could not be reproduced with succeeding doses of desoxycorticosterone and ascorbic acid or the response could be duplicated with the use of placebos. In no patient was there evidence of objective improvement, and in two patients there was progression of the disease with involvement of previously unaffected joints.

CONCLUSIONS

The use of desoxycorticosterone acetate with ascorbic acid had no specific value in the treatment of a series of patients with rheumatoid arthritis.

Temporary subjective improvement, noted in many instances, was as readily produced by the use of placebos as with the desoxycorticosterone and ascorbic acid regimen.

GENERALIZED TORULOSIS WITH BONE INVOLVEMENT

MORRIS F. WIENER, M.D.
MIAMI BEACH, FLA.

A UNIQUE case of systemic torulosis is reported in which clinically demonstrable skeletal lesions proved to be, on postmortem study, torulosis granuloma of the bone marrow. No case is found in the literature in which definite osseous lesions are described, although the skeletal system is mentioned *en passant* as one of the rare sites of systemic Torula (Cryptococcus) invasion.

REPORT OF A CASE

Present Illness.—P. S. (R-2369), a 53 year old white man, was admitted to the Medical Service of the Veterans Administration Hospital, Miami Beach, Fla., on Sept. 10, 1946, complaining of persistent headache, insomnia and visual disturbance of one month's duration.

Previous History.—In 1936, while in Colorado, he had an illness lasting about 30 days and manifested by fever, sweating, cough, anorexia and loss of weight. In 1937, when 44 years of age, he was hospitalized at Fitzsimons General Hospital, Denver, for about 75 days because of joint pains and a "nervous breakdown." Since 1940 the patient suffered increasing weakness, and since 1942 he had fever and chills at irregular intervals with occasional nocturnal vertigo and dyspnea. In July 1946 he had urinary dribbling for 10 days, followed by nocturia, eight times a night.

Physical Examination.—The general appearance indicated severe prolonged chronic illness. The temperature was 101 F.; the blood pressure was 85/60, and the pulse rate 72 per minute. The pupils reacted sluggishly to light, and the fundal disks were pale and poorly outlined. Hearing was diminished bilaterally. The inguinal, femoral and epitrochlear lymph nodes were palpable. On auscultation a few moist inspiratory basal rales and a precordial soft aortic systolic murmur were heard. Mild tenderness was present in the right costovertebral angle. Results of the remainder of the examination were essentially normal.

Laboratory Findings.—The blood count on admission showed 3,200,000 red blood cells, 58 per cent hemoglobin (Sahli) and 22,550 white blood cells, with 84 per cent polymorphonuclear forms, 10 per cent lymphocytes, 2 per cent monocytes and 4 per cent eosinophils. On Sept. 18, 1946 the red cell count was 2,600,000 and the white cell count 11,110, with 68 per cent polymorphonuclear forms, 30 per cent lymphocytes and 2 per cent eosinophils. Studies showed no malarial parasites. The urinalysis on admission disclosed a specific gravity of 1.010, a 1+ reaction for albumin and no casts. The diagnostic agglutinations were negative for typhoid H and O, paratyphoid, brucellosis and typhus antigens. The Kahn reaction was negative. The studies of sputums were negative for acid-fast bacilli. The blood urea nitrogen was 28 mg. per 100 cc. soon after admission and 14.2 mg. on October 28, when the alkaline phosphatase was 8.6 Bodansky units.

Roentgenologic studies on Sept. 10, 1946 showed normal heart and lungs; the lumbar portion of the spine and the pelvis exhibited definite osteoporosis. The skull was normal. On October 29 roentgen studies revealed small, rounded and ovoid osteolytic lesions in the lower part of the left

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Dr. Wiener was formerly pathologist at the Veterans Administration Hospital, Coral Gables, Fla.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

ilium, upper part of the humerus, head of the radius and proximal end of the right femur; possible malignant metastases were suggested.

Course in Hospital.—The headache remained unrelenting. The temperature declined to normal but rose on three occasions to 101 F. Treatment was supportive and symptomatic. Vertigo and vomiting were recurrent. Mental confusion and visual hallucinations developed. On the forty-first hospital day, Cheyne-Stokes breathing developed and the patient became unresponsive. He remained in this critical state for the next 10 days, when the chest filled with moist rales. Death occurred on the fifty-first hospital day.

The following clinical diagnoses were made: carcinoma, type and location undetermined, involutional melancholia and severe malnutrition.

Autopsy Observations.—An autopsy was performed 6½ hours post mortem (laboratory accession no. A-49-46), and the essential observations follow:

The body was that of a poorly nourished 53 year old man. The left eyeball was in midposition; the pupil was irregular in outline and slightly larger than that of the exophoric right

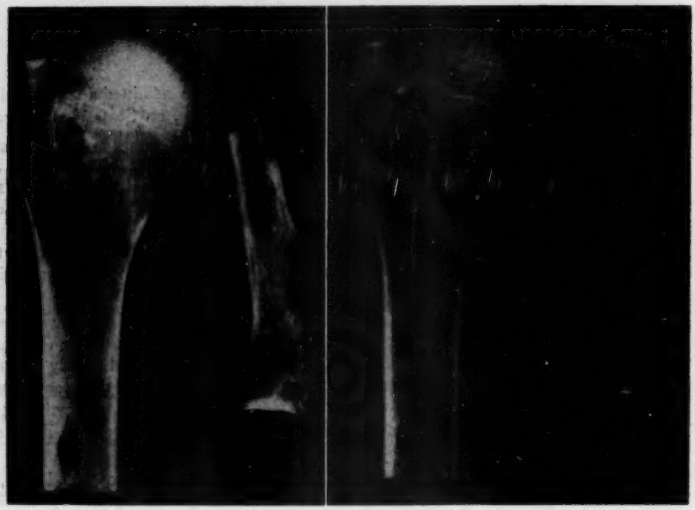

Fig. 1.—Roentgen view of humerus and radius showing round and ovoid osteolytic lesions. Negative no. 101821.

eye. The pleural cavities showed slight apical fibrinous adhesions, and the pericardial cavity had wide bands of easily broken adhesions.

The heart weighed 390 Gm. and showed focal epicardial fibrinous change anteriorly and laterally. The left ventricular myocardium contained a 3 mm. pale nodule. Microscopically, the thickened epicardium showed congestion and diffuse round cell infiltration; a focus of round cells, giant cells and epithelioid cells was noted.

The right lung showed absence of the middle lobe. The interlobar fissure anteriorly displayed six hard subpleural nodules on the lower surface. A 2 mm. subpleural cavity was seen in the lower lobe of the right lung, microscopically consisting of a fibrous wall and a lumen filled with pale mucinous-like substance containing hollowed, refractile, round bodies 4 to 9 microns in diameter and highly suggestive of Cryptococcus. Aeration and crepitation were fairly preserved in both lungs, with a small amount of pink froth expressed from the posterior aspects.

The spleen weighed 150 Gm. Microscopically, the trabeculae and vessel walls exhibited thickening by amyloid deposition (special stains).

The adrenal glands weighed 30 Gm. and microscopically showed granulomatous foci composed of giant cells, round cells and Cryptococcus cells.

The pancreas weighed 90 Gm. and was normal.

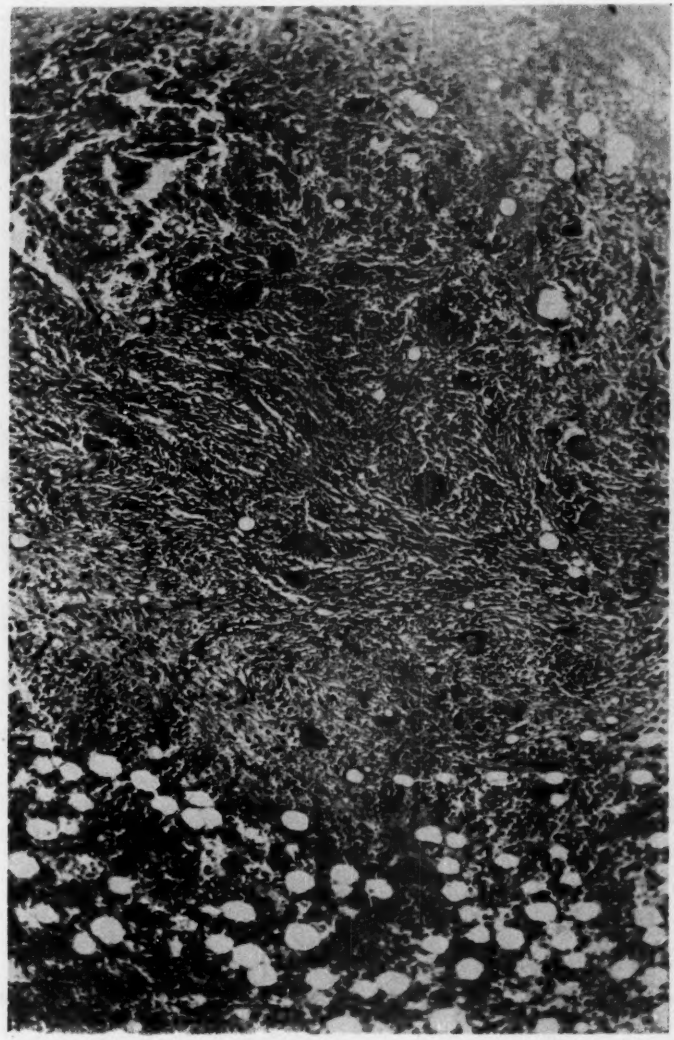

Fig. 2.—Photomicrograph of bone lesion (× 90), showing the granulomatous giant cell reaction. Negative no. 102966.

The liver weighed 2,200 Gm. The cut surfaces were of nutmeg appearance, and a nodule, 1 mm. in diameter, of yellow cheesy material was located. Microscopically, the sinusoids showed deposits of homogeneous red substance demonstrated to be amyloid by congo red stain.

The digestive tract was normal.

The kidneys were fairly similar, and each weighed 140 Gm. The upper half of the right kidney exhibited poor corticomedullary demarcation and microscopically displayed glomerular

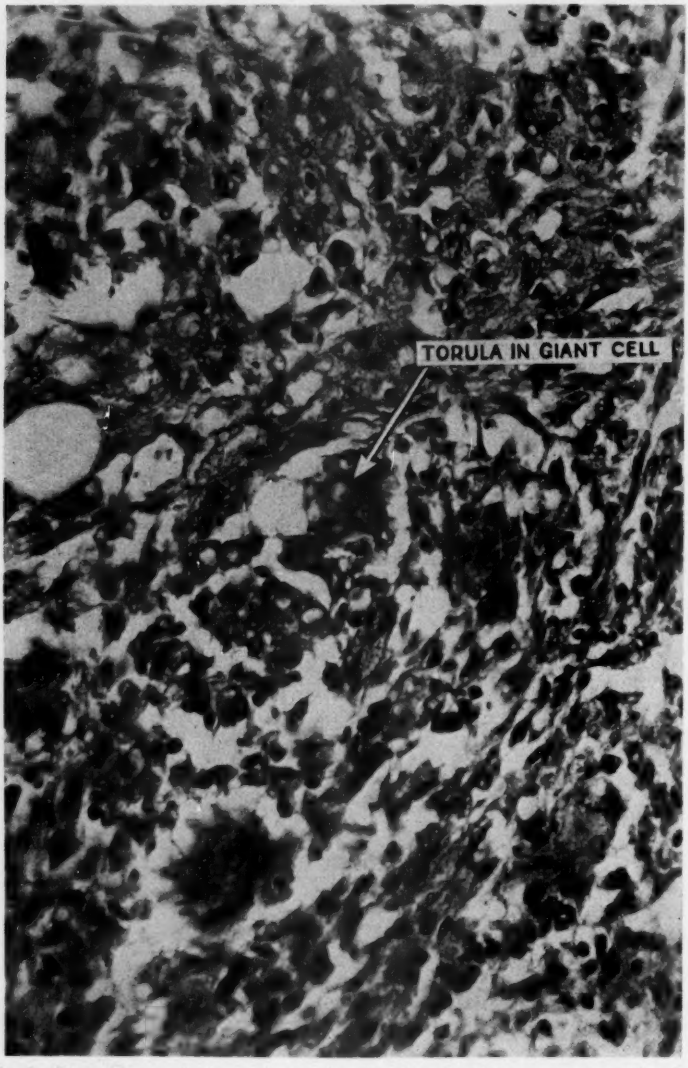

Fig. 3.—Photomicrograph of same bone lesion (fig. 2) under higher power (× 515), showing Torula cells both free and within giant cells. Negative no. 102963.

and tubular changes consistent with amyloid degeneration. The bladder was contracted; the greater portion of the mucosal lining was purplish black and microscopically showed mucosal

necrosis, leukocytic infiltration, congestion and cystic spaces lined by flattened cells. The seminal vesicles were dilated; the right was filled with cloudy viscid fluid under little pressure. Microscopically, section through the ampulla showed a granulomatous reaction of round cells and

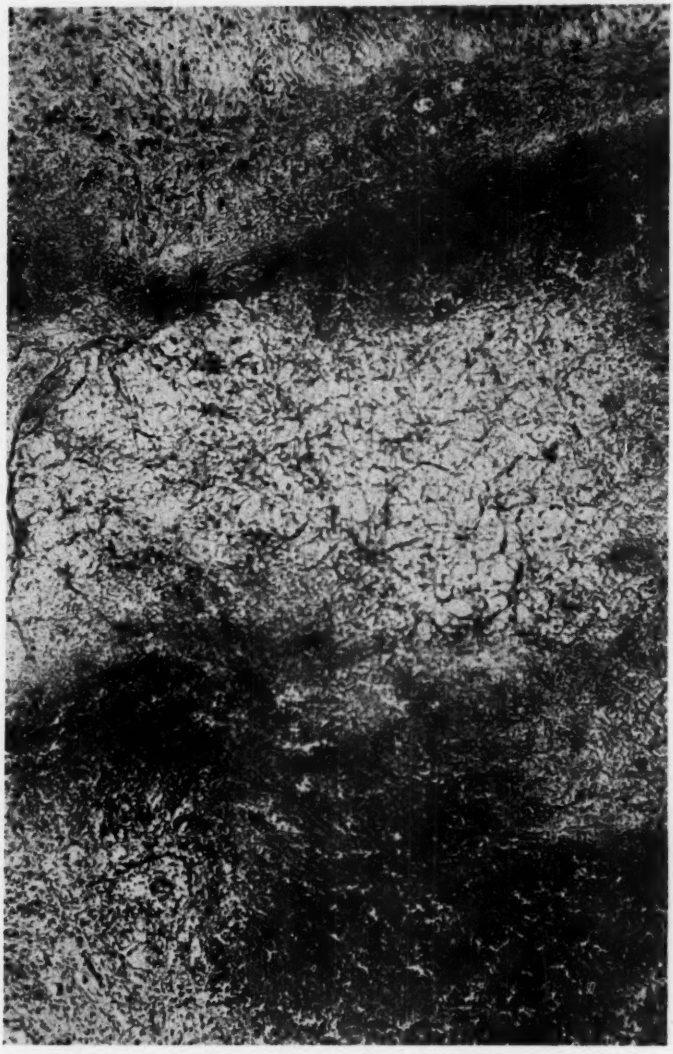

Fig. 4.—Photomicrograph of cerebral mucinous-like cystic lesion (low power, × 90). Negative no. 102965.

multinucleated cells with numbers of yeast forms; squamous metaplasia of the columnar epithelium was demonstrated in areas.

There were firm, discrete enlargements of the superficial inguinal, femoral and epitrochlear nodes and the deep mesenteric, periportal, mediastinal and peripancreatic nodes. A mediastinal and peripancreatic node showed suppuration. Microscopically, the nodes revealed loss of archi-

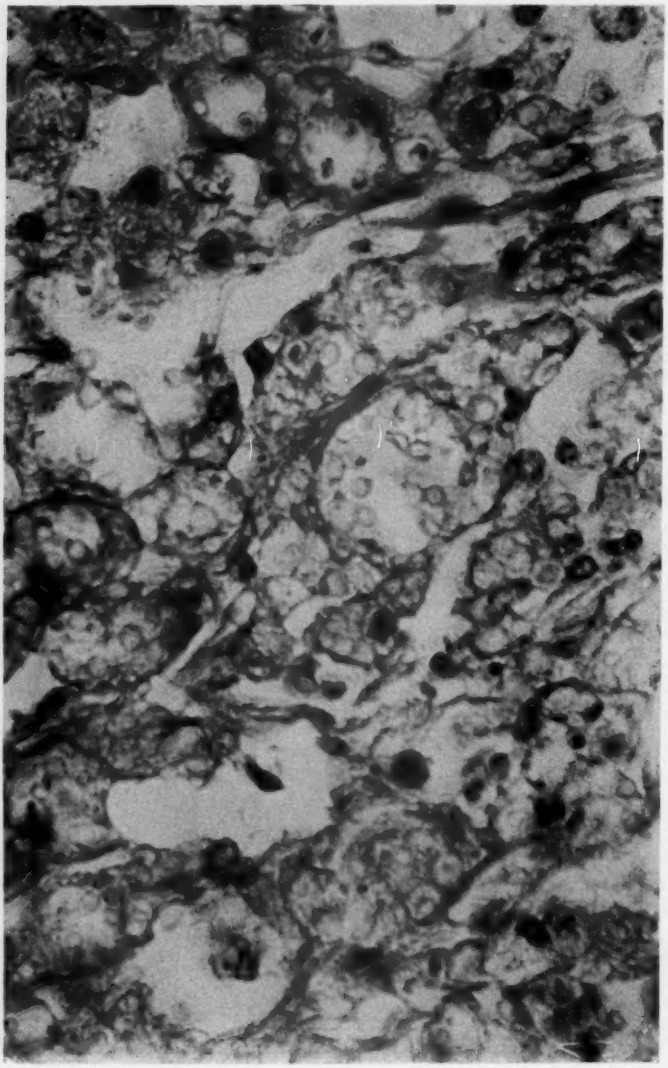

Fig. 5.—Photomicrograph of some cerebral lesion (fig. 4) under high power (× 1,000) showing numerous Torula cells. Negative no. 102967.

tecture and a granulomatous process composed of small mononuclear and giant multinuclear cells, epithelioid cells and yeast forms; there were areas of curled homogeneous pink material and thickened vascular walls giving a positive stain with congo red.

Sections through the head of the radius and upper part of the humerus showed rounded, pallid, gray-red gelatinous areas measuring up to 2 cm. in diameter (fig. 1). Microscopically, these foci consisted of highly cellular granulomatous lesions displaying round cells, giant cells and yeastlike bodies morphologically characteristic of Torula cells (fig. 2); destruction of the bone trabeculae and replacement of the marrow tissue by the granulomatous process were demonstrable.

The brain and meninges presented striking changes. The leptomeninges showed focal mucinous-like thickening over the right and left frontoparietal regions. The left cerebral hemisphere on section exhibited a translucent cystlike focus 2 cm. in diameter in the premotor area involving both the gray and the white matter. Microscopically, sections through the soft, pale translucent areas disclosed cystic spaces surrounded by epithelioid cells, epithelioid macrophages, small mononuclear and large multinucleated round cells and scattered plasma cells (fig. 3). Large numbers of rounded hollowed bodies, similar to those in the lung, were seen within giant cells and freely scattered among the epithelioid and round cells (fig. 4). The leptomeninges and parenchyma revealed nonsuppurative foci of histiocytes and giant cells. The brain showed intense inflammatory perivascular infiltration, dilated Virchow-Robin spaces and "cystic" parenchymal defects.

Bacteriologic Studies.—Smears of exudate from meninges revealed no bacteria by Gram or acid-fast stains. Cultures on blood agar yielded no growth at 48 hours. Unfortunately, the culture was accidentally discarded prematurely. A review of the smear from the meninges stained by Ziehl-Neelsen method showed organisms characteristic of Cryptococcus. Anatomic diagnoses were as follows:

Central nervous system
- Granulomatous leptomeningoencephalitis due to torulosis (Cryptococcus)

Respiratory system
- Pulmonary torulosis
- Chronic bronchitis
- Pulmonary congestion
- Agenesia of middle lobe of right lung
- Pleural fibrinous adhesions

Skeletal system
- Myeloid granulomas of torulosis
  - a. Humerus
  - b. Radius
  - c. Femur
  - d. Ilium
- Old fracture, right lower tibia

Cardiovascular system
- Focal granulomatous myocarditis (probable Torula)

Genitourinary system
- Renal amyloidosis
- Cystitis cystica
- Seminal granulomatous vesiculitis of torulosis
- Squamous metaplasia of seminal vesicle
- Chronic, mild prostatitis

Lymphatic system
- Lymphogranulomatosis of torulosis
  - a. Mediastinal
  - b. Peripancreatic
- Periportal lymph node amyloidosis
- Lymphadenopathy, superficial, epitrochlear and femoral

Spleen
- Amyloidosis

Adrenal glands
- Torulosis granuloma

Comment.—This is a case of a 53 year old white man giving a history of recurring fever over the past 10 years and severe persistent headache of 30 days' duration. On admission he was seen to be chronically and severely ill. Superficial lymphadenopathy, pallor, indistinct optic disks and low grade fever were present. Late in the course, roentgen studies showed osteolytic bone changes, and a clinical diagnosis of undetermined carcinoma was made. Ominous respiratory changes developed 10 days before death on the fifty-first hospital day.

Necropsy showed systemic mycosis of Cryptococcus neoformans (torulosis) mainly involving the brain and leptomeninges, bone and lymph nodes, with probable origin from a nodular pulmonary infection. Secondary visceral amyloidosis was present.

COMMENT

Brief Survey of the Literature.—Stoddard and Cutler [1] are duly credited with clearly distinguishing (1916) torulosis from two other mycotic diseases, blastomycosis (due to Blastomyces hominis) and coccidioidomycosis (due to Coccidioides immitis). The suggestion is theirs that the organism be called Torula histolytica, because of the local histolytic action presumably induced by this yeastlike fungus. In 1923 Freeman and Weidman [2] described the cultural characteristics of Torula and drew up a classification. A survey of 43 cases was reported by Freeman [3] in 1931. The curious relationship of torulosis to Hodgkin's disease was seriously considered by Fitchett and Weidman [4] in 1934 and by Mitchell [5] in 1936. Tinney and Schmidt [6] in 1944 called attention to an important and unexplained frequency with which Torula meningitis and Hodgkin's disease are associated. Wade and Stevenson [7] noted coincidental lymphoblastoma and Torula meningitis in four cases and Mallory [8] in five cases. The simultaneous occurrence of these two rare diseases appears to exceed the mathematical law of coincidence. Levin [9] in 1937 searchingly studied 60 cases of torulosis. Reeves, Butt and Hammack [10] in 1941

1. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man: A Group of Cases, Characterized by Chronic Lesions of the Central Nervous System, Monograph 6, New York, Rockefeller Institute of Medical Research, Jan. 13, 1916.

2. Freeman, W., and Weidman, F. D.: Cystic Blastomycosis of the Cerebral Gray Matter Caused by Torula Histolytica, Stoddard and Cutler, Arch. Neurol. & Psychiat. **9**:589-603 (May) 1923.

3. Freeman, W.: Torula Infection of the Central Nervous System, J. Psychol. u. Neurol. **43**:236-345 (Nov.) 1931.

4. Fitchett, M. S., and Weidman, F. D.: Generalized Torulosis Associated with Hodgkin's Disease, Arch. Path. **18**:225-244 (Aug.) 1934.

5. Mitchell, L. A.: Torulosis, J. A. M. A. **106**:450-452 (Feb. 8) 1936.

6. Tinney, W. S., and Schmidt, H. W.: Torula Infection, M. Clin. North America **28**:950-956 (July) 1944.

7. Wade, L. J., and Stevenson, L. D.: Torula Infection, Yale J. Biol. & Med. **13**:467-476 (March) 1941.

8. Mallory, T. B.: Discussion, New England J. Med. **210**:1292-1294 (June 14) 1934.

9. Levin, E. A.: Torula Infection of the Central Nervous System, Arch. Int. Med. **59**:667-684 (April) 1937.

10. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System: Report of 6 Cases with 3 Autopsies, Arch. Int. Med. **68**:57-79 (July) 1941.

reported six more and brought the total number then to 79. A comprehensive review of torulosis was made in 1946 by Voyles and Beck,[11] who added four new cases of their own and brought the total reported in the literature to 108 cases, with

Summary of Cases According to the Schema of Levin *

	Levin	Binford 1940	Beck-Voyles 1945	Total
Sex of patient:				
Male	39	9	23	71
Female	20	4 †	13 †	37
Age distribution in years:				
Under 10	1	2	1	4
10-19	6	1	4	11
20-29	9	3 †	9	21
30-39	9	3	8	20
40-49	15	1	4	20
50-59	16	1	7	24
60-69	2	2	2	6
Not stated	2	0	0	2
Duration of illness in months:				
0-1	3	3	3	9
1	6	0	1	7
2	10	3	6	19
3	9	1	5	15
4	8	0	5	13
5	3	1	2	6
6	3	2	1	6
7	1	0	1	2
8	2	0	0	2
9	1	0	1	2
10-12	1	0	1	2
13-24	3	0	1	4
25-36	5	0	1	6
37-48	0	1	1 †	2
49-60	0	1	0	1
61-72	1	0	0	1
Unknown	4	0 †	7	11
Organs involved including the central nervous system:				
Lungs	9	4	7	20
Generalized	8	1	6	15
Kidney	2	2	8	12
Spleen	1	1	3	5
Adrenal glands	1	1	5	7
Abdominal nodes	1	0	3	4
Peribronchial nodes	1	0	1	2
Tonsil	3	0	0	3
Subcutaneous tissue	2	0	2	4
Skin	5	0	1	6
Central nervous system only	30	4 †	20	54
When diagnosed:				
Post mortem	23	8	6	37
Ante mortem	37	5 †	29 †	71
How diagnosed:				
Antemortem cultures only	10	4 †	26 †	40
Biopsy of brain ante mortem	2	1	5	8
Postmortem histologic sections	22	0	4	26
Cultures and postmortem histologic sections	26	0	1	27

* From Voyles and Beck.[11]
† These cases appeared in Binford's review but were advanced to the next column in duplicate with correction in number.

11. Voyles, G. Q., and Beck, E. M.: Systemic Infection Due to Torula Histolytica (Cryptococcus Hominis): Report of 4 Cases and Review of the Literature, Arch. Int. Med. **77**:504-515 (May) 1946.

a comprehensive analysis according to Levin's schema.[9] More recently, Prezyna [12] reported a case in which the diagnosis was not definitely established until necropsy study.

MYCOLOGIC CHARACTERISTICS

Torula histolytica is yeastlike in that it reproduces by budding only. It is classified with the "fungi imperfecti" because no generally accepted description of a life cycle has been recorded. This organism is widely disseminated in nature and is found on trees, flowers, fruits and insects. Many of the Torula are nonpathogenic. Cryptococcus neoformans and Debaryomyces hominis are terms recently introduced by bacteriologists for Torula histolytica. The disease is also known as European blastomycosis (Ash [13]). The micro-organism of torulosis is characteristically spheroid or oval and varies greatly in size, from 2 to 25 microns. Ultramicroscopic forms have been suggested.[4] There is a consistent absence of myceliums or spore formation both in direct smears from a lesion and in cultures, and sugar fermentation is feeble or absent. The numerous nonpathogenic varieties usually ferment sugar. The organism has a typical double contour which is readily seen with sodium hydroxide or india ink preparations. Typical Torula lesions are produced in mice and rats inoculated subcutaneously or intraperitonally with heavy saline suspension of a 36 hour culture, the animals dying in five to eight days.

Sabouraud slants grow out small, round, smooth, cream-colored colonies within 48 hours, which coalesce and evenly spread out over the surface of the medium. The cultures darken after one week and later develop a dry-looking surface.

Freeman's classification [3] of three species is rendered insecure by the significant observations of Longmire and Goodwin,[14] who noted the pleomorphism of the Torula in culture, experimental animals and actual human lesions.

Culture has been obtained from spinal fluid and sputums and in one case was reported recovered from urine [3]; blood and lymph node aspirations are also noted as possible sources. The finding of yeastlike bodies in the sputum, even though suggestive of torulosis, cannot be considered diagnostic until their pathogenicity has been determined by animal inoculation.

PORTAL OF ENTRY

The precise mode of infection by Torula histolytica continues to remain obscure, although many suggested possibilities are referred to in the literature. Clinical and experimental deductions are inconsistent. Infection of the meninges through the nasopharynx, tonsils, middle ear or paranasal sinuses is suggested by demonstrated lesions about the gasserian ganglion in cases reported by Hall [15] in 1928, by Hirsch

12. Prezyna, A. P.: Cryptococcus Neoformans Meningo-Encephalitis: Report of a Fatal Case, U. S. Armed Forces M. Bull. **1**:866-873 (Aug.) 1950.

13. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases: An Atlas, Philadelphia, W. B. Saunders Company, 1945.

14. Longmire, W. P., Jr., and Goodwin, T. C.: Generalized Torula Infection: Case Report and Review with Observations on Pathogenesis, Bull. Johns Hopkins Hosp. **64**:22-43 (Jan.) 1939.

15. Hall, G. W.; Hirsch, E. F., and Mock, H. E.: Torula Histolytica Meningo-Encephalitis, Arch. Neurol. & Psychiat. **19**:689-694 (April) 1928.

and Coleman [16] in 1929 and by many authors who favor the respiratory route. The intestinal path of entry is mentioned by Fitchett and Weidman,[4] who recall Tanaka's [17] observation that 10 per cent of apparently normal mesenteric lymph nodes at autopsy showed Saccharomyces, and thereby imply that the biologic characteristics of yeast cells are consistent with enteric portal of entry by Torula. In a case reported by Johns and Attaway [18] the initial lesion, a superficial granuloma resulting from a razor cut, was followed by meningitis with the characteristic Torula organisms found in the spinal fluid. Kessel and Holtzwart [19] in 1935 reported on studies with a Torula recovered from a knee joint infection and from subsequent lesions in the nipple region; in this case meningitis of undetermined origin developed, with recovery. Wade and Stevenson [7] were unable experimentally to produce involvement of the central nervous system without visceral involvement, regardless of the route of the inoculation, thus indicating that all cases of central nervous system torulosis are probably preceded by blood stream invasion.

PATHOLOGICAL ASPECTS

The remarkable affinity of Torula histolytica for the central nervous system is fairly emphasized in the literature. The brain is involved in all cases of internal torulosis. The tissue response to Torula invasion varies greatly, particularly in the brain and meninges. Experimentally, Longmire and Goodwin [14] have shown a minimal reaction in susceptible mice that died within five to eight days with generalized torulosis cysts, whereas the more resistant white rats, similarly inoculated, died or were killed six to eight weeks later and showed epithelioid tubercles and granulomatous inflammation. A correlation was made between the smaller-sized Torula and the corresponding inconspicuous cellular response and poor defense reaction, in contrast to the larger-sized Torula with the prominent tubercle formation and greater reaction. These workers also pointed out variation in the degree of resistance offered to the fungus from tissue to tissue in different areas of the same organ and variability of general resistance in different persons.

Crone, DeGroat and Wahlin [20] noted this variation in the type of tissue reaction in human torulosis:

> The degree and character of the inflammatory response that the torula excites seem to vary greatly in different human cases. It may be feeble or absent, proliferative, or occasionally exudative, and its character cannot be explained by the age of the lesion. In our experimental animals the inflammatory response seemed to be almost entirely histiocytic and its degree related to the local supply of cells capable of being mobilized as macrophages. Few in the brain, such cells were more numerous in the lung and peritoneum. The same general statement, applied to human material, would be an exaggeration, although not an excessive one.

16. Hirsch, E. F., and Coleman, G. H.: Acute Miliary Torulosis of the Lungs, J. A. M. A. **92**:437-438 (Feb. 9) 1929.

17. Tanaka, T.: Saccharomyces in Mesenteric Glands of Human Body, J. Path. & Bact. **23**:350 (June) 1920.

18. Johns, F. M., and Attaway, C. L.: Torula Meningitis: Report of Case and Summary of Literature, Am. J. Clin. Path. **3**:459-465 (Nov.) 1933.

19. Kessel, J. F., and Holtzwart, F.: Studies with Torula from a Knee-Infection in Man, Am. J. Trop. Med. **15**:467-483 (July) 1935.

20. Crone, J. T.; DeGroat, A. F., and Wahlin, J. G.: Torula Infection, Am. J. Path. **13**:863-879 (Sept.) 1937.

Kessel and Holtzwart [19] raised the question of tissue selectivity of different strains of Torula. The lesions of torulosis might better be explained on the basis of virulence of the strain and resistance and hypersensitivity of the host. Urbach and Zach [21] demonstrated factors of allergy and immunity in the pathogenesis of torulosis similar to that in tuberculosis. There is no specific histopathological change induced by Torula histolytica and the yeastlike forms with buds.

The macroscopic picture in the brain may be that of (*a*) a diffuse meningitis, at times basal and suggestive of tuberculosis, (*b*) encephalitis or meningoencephalitis or (*c*) Torula cysts which simulate cerebral tumor, as in the two cases reported by Swanson and Smith.[22] The cystic tumor of Torula granuloma does not empty itself when opened and thus sharply differs from true cystic tumors. These authors also point out the isolated character and sharp demarcation of the Torula cyst from the adjacent cortex, the latter not showing any reaction. The similarity of the Torula cyst to metastatic mucinous carcinoma is obvious.

The lungs may show nodules composed of giant cells with Torula and marked peripheral round cell infiltration, as in the case described by Longmire and Goodwin [14] and the case reported herein. The pulmonary alveoli may be packed with Torula. Multiple cavities in the lower lobe are described in the case reported by Tinney and Schmidt,[6] although increased hilar markings and parenchymal calcification are more frequently noted. There may be large numbers of Torula cells in the alveoli with scarcely any reaction present or with only a slight mononuclear response.

Torulosis of the skin, according to Wile,[23] may occur as acneform pustules, granulomatous ulcers, deep-seated abscesses and subcutaneous and deep-seated nodules. The nodules may attain the size of a hand, with no tendency to ulcerate. Histopathologically, a discrete atypical caseous granulomatous process and large numbers of giant cells are seen. The Torula cells may be exceptionally numerous and may exist free or within giant cells. Little is known of the clinical course in the early stages, since the disease is rarely diagnosed until meningitis is well established.

CLINICAL PICTURE

The commonest symptom is severe headache, a fact in keeping with the constant involvement of the central nervous system. The headache may be insidious, progressive, persistent and severe. The headache, which almost always interferes with sleep, may be frontal, and, as in the case associated with Hodgkin's disease reported by Tinney and Schmidt,[6] may be aggravated by head bending, stooping, coughing or sneezing. Projectile vomiting may be present. No localizing features are associated with the increased intracranial tension. Vomiting, vertigo, stiffness of the neck, visual disturbances and tinnitus may be part of the protean and often confusing picture. Psychosis in the presence of normal results on blood and spinal fluid studies further increases the difficulty of accurate diagnosis. Brain tumor, brain abscess, tuberculous meningitis, encephalitis or paresis may be suspected. The temperature

21. Urbach, E., and Zach, F.: Generalisierte Torulose, Arch. Dermat. u. Syph. **162**:401-421, 1930.

22. Swanson, H. S., and Smith, W. A.: Torula Granuloma Simulating Cerebral Tumor: Report of 2 Cases, Arch. Neurol. & Psychiat. **51**:426-431 (May) 1944.

23. Wile, U. J.: Cutaneous Torulosis, Arch. Dermat. & Syph. **31**:58-64 (Jan.) 1935.

may be only slightly elevated or even normal, despite the extensive tissue destruction by an infectious agent involving multiple systems. The white blood cell count may be normal.

The pulmonary signs and symptoms may simulate those of tuberculosis. The demonstration of yeastlike bodies in the sputum morphologically characteristic of Torula cannot be considered diagnostic until pathogenicity is proved by animal inoculation (mouse, white rat, guinea pig). Various chronic diseases seem to increase the susceptibility to fungous infection. This is suggested by reported cases of generalized torulosis complicating tuberculosis, Hodgkin's disease and carcinoma.

DIAGNOSIS

Clinically, torulosis can be proved in many cases in which the condition is at all suspected. Voyles and Beck's [11] analysis discloses 71 cases of torulosis diagnosed clinically in a total of 108 (66 per cent), showing increasing awareness of the existence of the disease. The possible presence of Torula meningitis must be considered in all cases of slowly progressive meningeal or cerebral excitation and increased intracranial pressure, after the diagnoses of tuberculosis, syphilis and tumor of the brain have been excluded. The diagnosis should be considered in all cases of obscure cerebrospinal disease, particularly those characterized by severe headache of undetermined orgin. The diagnosis can be made ante mortem in these cases only by the identification of the causative agent in the spinal fluid.

SPINAL FLUID

The rapid settling out of sediment should arouse suspicion of the presence of large numbers of Torula cells in the spinal fluid. As the fluid runs into the tube from the lumbar puncture needle, it appears gray and cloudy, but, instead of remaining so for some hours, most of the solid matter settles to the bottom within 10 minutes, giving the tube the appearance of having been centrifuged.[14]

In a suspected case a drop of sediment (centrifuged if necessary) is mixed with a drop of Greenthal's stain on a slide, covered with a cover slip and examined: The Torula cells show a definite "cellulose-like" wall surrounded by a wide purplish or bluish capsule.[24] Budding forms may be seen. This strain will definitely betray the leukocytes by the stained nucleus and cytoplasm, neither of which is present in the Torula cells; the latter otherwise are easily mistaken for lymphocytes. Cultures are prepared by Sabouraud inoculation of the suspected material (spinal fluid sediment, bronchial secretion, blood, urine or aspirated tissue). Torula reproduces by budding only, never forms myceliums and ferments sugar weakly or not at all. India ink preparations are effective. Animal inoculation is necessary to establish pathogenicity conclusively in the case of suspected Torula cells found in sputums, bronchial secretion or cutaneous lesions.

TREATMENT

No specific remedy is known. The alleged beneficial effects of potassium iodide and sulfadiazine, singly and in combination, have not been confirmed by the animal

24. Magruder, R. G.: A Report of 3 Cases of Torula Infection of the Central Nervous System, J. Lab. & Clin. Med. **24**:495-499 (Feb.) 1939.

studies of Beck and Voyles.[25] The apparently successful result with high voltage roentgen therapy to Torula infection of the breast is mentioned by Kessel and Holtzwart.[19] It must be remembered, however, that while the duration of the disease is not known a case reported by Reeves, Butt and Hammack[10] persisted more than seven years eight months. In this case, a 21 year old woman was treated with both iodides to the limit of tolerance and Torula antigen prepared by Dr. Kreuger, of the University of California (Berkeley). Repeated lumbar puncture to relieve the increased intracranial pressure and acriflavine, 1:10,000 solution given daily intrathecally, were used by Shapiro and Neal.[26] Recovery from Torula histolytica meningoencephalitis following bilateral mastoidectomy and sulfonamide therapy was reported by Marshall and Teed in 1942.[27] In any chronic disease that may have spontaneous remissions, the claim of ultimate cure cannot be assured. The value of treatment with penicillin, streptomycin or other antibiotics in torulosis is as yet undetermined, although Collins[28] states that protoanemonin is effective in vitro.

PROGNOSIS

Of the recorded 108 cases reviewed by Voyles and Beck,[11] survival was no longer than four months after the onset of the disease in 43 cases, or 40 per cent, and no longer than two months in 32 per cent. In seven cases the patients were still living at the time of the report. The authors state that "the course of infection may be fulminating or chronic and that if the patient survives the initial acute phase, the duration of illness may be two to three years." Cases are reported suggesting the possibility of recovery.[19]

SUMMARY

A case of generalized torulosis with osseous invasion is presented in which the diagnosis is based on microscopic study at necropsy and direct smear of meninges. This appears to be the only case reported in which osseous lesions were demonstrated by roentgenography and photomicrography of torula cells in bone marrow.

A brief survey of the literature is made, and the mycologic features, portal of entry, pathological aspects, diagnosis, treatment and prognosis are reviewed.

ADDENDUM

Since this paper went to press, my attention has been called to an interesting collection of 20 cases of torulosis with bone involvement.[28] A number of these cases appear to be of cortical bone erosion due to direct extension from Torula soft tissue granuloma. In several of the other cases reported, the etiological basis is open to discussion. My three cases are not debatable.

The illustrations appear through the courtesy of the Armed Forces Institute of Pathology.

25. Beck, E. M., and Voyles, G. Q.: Systemic Infection Due to Torula Histolytica (Cryptococcus Hominis): II. Effect of Chemotherapeutic Agents in Experimentally Produced Infections, Arch. Int. Med. **77**:516-525 (May) 1946.

26. Shapiro, L. L., and Neal, J. B.: Torula Meningitis, Arch. Neurol. & Psychiat. **13**:174-190 (Feb.) 1925.

27. Marshall, M., and Teed, R. W.: Torula Histolytica Meningoencephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy; Preliminary Report, J. A. M. A. **120**:527-529 (Oct. 17) 1942.

28. Collins, V. P.: Bone Involvement in Cryptococcosis (Torulosis), Am. J. Roentgenol. **63**:102-112 (Jan.) 1950.

Case Reports

NONSPECIFIC PERICARDITIS

A Fatal Case

MALCOLM C. McCORD, M.D.
AND
JAMES T. TAGUCHI, M.D.
DAYTON, OHIO

IN THE past 10 years there has been increased recognition of a form of pericarditis of unknown origin variously termed as idiopathic, nonspecific, viral or benign.[1] Attention also has been focused on the difficulties of differentiating this disease from acute myocardial infarction.[2] The importance of such differentiation is quite apparent from both a prognostic and a therapeutic standpoint.

The following case of acute idiopathic pericarditis is reported because of a fatal outcome in a supposedly benign condition and the possible detrimental effect of the anticoagulant therapy administered.

REPORT OF CASE

A 52 year old white man was admitted to the Medical Service of the Veterans Administration Hospital, Dayton, Ohio, at 5:00 p.m. on July 11, 1950, with a chief complaint of pain in the chest.

The patient had been in good health until 36 hours prior to admission. After ingestion of a large breakfast, there was an onset of severe pain under the upper half of the sternum. The pain was sharp and oppressive in character. Shortly after the onset the pain spread to the entire retrosternal area. There was radiation to the back of the neck, to the left shoulder and down the left arm to the wrist. The pain was aggravated by respiratory movements. There was no air hunger, orthopnea or cough. The pain was constant and was not relieved by rest. The patient was seen at home by his physician on two occasions, 12 and 24 hours after the onset of his illness. On each occasion he was given an injection of morphine and atropine, with only temporary and partial relief of pain. Owing to the severity of the pain, the patient was brought to the hospital.

The past history revealed no previous occurrence of pain in the chest, no known heart disease and no episodes of pneumonitis or recurrent infections of the upper respiratory tract. Blood pressure determinations in the past were said to be hypotensive. In 1918 and again in 1939 there were episodes of eczematoid dermatitis of the hands. After a hemorrhoidectomy in

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From the Medical Service, Veterans Administration Center.

Dr. McCord is Fellow in Cardiology, and Dr. Taguchi is Chief of the Department of Cardiology.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Logue, R. B., and Wendkos, M. H.: Acute Pericarditis of Benign Type, Am. Heart J. **36**:587, 1948.

2. Barnes, A. R., and Burchell, H. B.: Acute Pericarditis Simulating Acute Coronary Occlusion, Am. Heart J. **23**:247, 1942. Wolff, L.: Acute Pericarditis Simulating Myocardial Infarction, New England J. Med. **230**:422, 1944.

1948, a severe dermatitis appeared which was thought to be a result of sensitivity to mercurial antiseptics. Two months after initial clearing the dermatitis recurred, requiring further hospitalization. Also, angioneurotic edema and urticaria had occurred on several occasions after the administration of barbituates.

Physical examination on admission revealed an acutely ill, apprehensive, well nourished man. The temperature was 98.8 F., the pulse rate 84, the respiration rate 28 per minute and the blood pressure 100/75. There was neither cyanosis nor pallor. The vessels of the optic fundi were normal. There was no distention of the neck veins. The chest was resonant to percussion and on auscultation; normal vesicular breath sounds were heard. The heart was not enlarged to percussion, and normal sinus rhythm was present. The heart sounds were distant in character, and the pulmonary second sound was of greater intensity than the aortic second sound. No murmur, gallop rhythm or friction rub was heard. The abdomen was distended and tympanitic, but there was no tenderness or rigidity. Rectal examination revealed a postoperative anal stricture. Peripheral vessels were not sclerotic, and pulsations were easily palpated.

Initial laboratory studies showed a white blood cell count of 14,600 per cubic millimeter, with 75 per cent polymorphonuclear cells. The blood sedimentation rate was 6 mm. per hour. A chest roentgenogram made with a portable apparatus demonstrated the heart to be of normal size and configuration and revealed minimal congestive changes of the base of the left lung. An electrocardiogram showed no abnormalities.

A diagnosis of acute myocardial infarction was made. Morphine and atropine were administered, with satisfactory diminution of pain. Anticoagulant therapy was instituted on the evening of admission, with administration of 300 mg. of bishydroxycoumarin (dicumarol®) by mouth and 100 mg. of heparin intramuscularly. Treatment with heparin was continued in doses of 50 mg. every four hours for 48 hours. Bishydroxycoumarin was given in sufficient amounts to maintain the prothrombin time at less than 25 per cent of normal for 14 days. The prothrombin level fell to 6.5 per cent of normal on one occasion.

On the second hospital day the pain in the chest was less severe. The patient's temperature rose to 100.8 F. On the third day a harsh to and fro pericardial friction rub was heard over a wide area at the base of the heart. An electrocardiogram at this time showed little change from the initial tracing other than an elevation of the S-T segment in lead I of 0.5 mm. (fig. 1). The pericardial friction rub persisted with decreasing intensity for three days. Supraventricular tachycardia developed on the fourth day of hospitalization with a regular rate of 150. The tachycardia reverted to sinus rhythm following oral administration of 24 grains (1.55 Gm.) of quinidine sulfate in a period of eight hours.

From the fifth until the twelfth hospital day the patient was afebrile and asymptomatic at rest in bed. At this time it was felt that the correct diagnosis was idiopathic pericarditis, but because of dissenting opinions the anticoagulant therapy was continued with the feeling that it would be of possible value. The white blood cell count decreased to 10,100 per cubic millimeter, and the blood sedimentation rate rose to 33 mm. per hour. The blood pressure remained at 110/80. Electrocardiograms showed a return of the minimally elevated S-T segment in lead I to the base line; however, notching of the T waves appeared in the unipolar precordial leads, and pronounced clockwise rotation of the heart developed (fig. 1). A second roentgenogram of the chest demonstrated no change in the heart size. The lung fields were clear.

On the twelfth hospital day, immediately after being taken to the x-ray department, the patient became weak, dizzy and nauseated. The blood pressure fell to 94/70, and the temperature rose to 100 F. During the night there was a recurrence of pain in the chest of the same nature as that present on admission. This persisted throughout the remainder of the hospital course. On the fourteenth hospital day supraventricular tachycardia with a rate of 160 reappeared. The electrocardiographic pattern was the same as that during the initial episode of tachycardia. The blood pressure was 84/70 with marked pulsus paradoxus, no sounds being audible below the sphygmomanometer cuff during inspiration.

The patient presented a picture of shock, with cyanosis, cool extremities, perspiration and anxiety. The heart was not enlarged, and a friction rub was not heard. A few moist rales were present at the bases of both lungs posteriorly. Oxygen was given by tent and nasal catheter. Quinidine sulfate was given in 6 grain (0.4 Gm.) doses every two hours for five doses. There

was no change in the cardiac rhythm or the clinical state. Lanatoside C, 1.6 mg., was administered intravenously. One hour later sinus rhythm returned, and the peripheral vascular collapse was less pronounced. On the following day the patient relapsed into a state of severe shock with cold pulseless extremities. Whole blood, 500 cc., was administered intra-arterially. Two hours later, cyanosis disappeared and the blood pressure returned to measurable levels. On the sixteenth hospital day the patient was moderately comfortable and maintained a blood pressure of 106/90. In the evening the patient removed the oxygen tent, walked across the hall to the washroom, collapsed and died immediately.

An autopsy was performed eight hours after death. On opening the thoracic cavity, approximately 250 cc. of amber-colored fluid was present in each pleural cavity. The pericardium was dark purplish red. On incision, dark red blood welled up from the pericardial cavity as though under moderate pressure. Approximately 150 cc. of free blood was present in multiple loculated

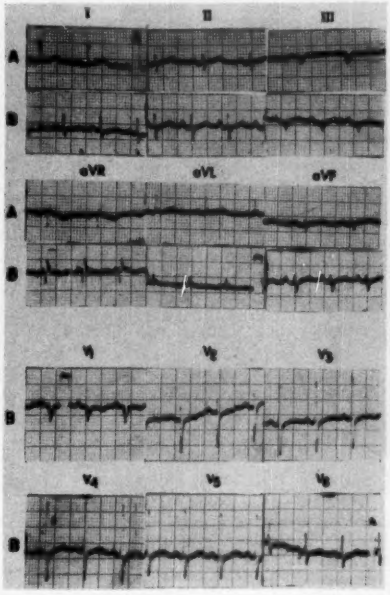

Fig. 1.—Tracings marked *A* were taken on the third hospital day at the time a pericardial friction rub was present. There is minimal elevation of the S-T segment in lead I. Tracings marked *B* were taken on the eleventh hospital day. These show notching of the T waves in the precordial leads.

areas in the pericardial cavity. The pericardium was greatly thickened, and the visceral and parietal layers were densely adherent except in the loculated areas of free blood described above. On peeling away the parietal pericardium, a shaggy, fibrinous, hemorrhagic surface was seen. The blood and fibrinous exudate in the pericardium extended around the base of the aorta and pulmonary artery. On examination of these vessels, the intima was seen to be smooth, no atheromatous plaques were present and there was no defect in the intima or evidence of dissection of the wall of the vessels. Epicardial fat was abundant in most areas, with some extension into the myocardium. The myocardium was of normal thickness and consistency and dark brownish red. There was no dilatation of the heart chambers. The cardiac valves were normal. There were several small subendocardial hemorrhages present in the right auricle. The coronary

arteries were dissected and found to be thin walled, smooth and patent throughout, with no evidence of rupture or aneurysmal dilatation. The lungs showed congestion, and frothy fluid was present in the bronchi. Cut section of the liver revealed prominent lobular markings.

Microscopic examination of the pericardium (fig. 2) revealed a heavy fibrinous deposit on the visceral pericardium enmeshing many clumps of red blood cells. A heavy infiltrate of lymphocytes and occasional polymorphonuclear cells were present. There was proliferation of fibroblastic tissue into the fibrin and clotted blood. In those areas of the myocardium separated from the pericardium by the epicardial fat, there was a relatively normal cellular pattern. In the areas of the myocardium directly contiguous with the pericardium, there was seen a heavy interstitial infiltration of lymphocytes with frequent polymorphonuclear cells. There were separation and fragmentation of the cardiac muscle fibers in these areas.

Microscopic examination of the lungs revealed the vessels to be congested and the alveoli filled with fluid. The sections of the liver disclosed dilated central veins and necrosis of the

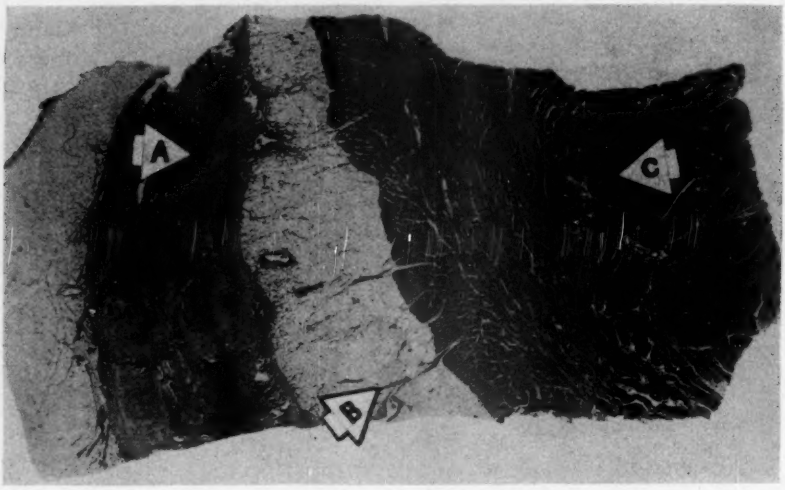

Fig. 2.—Microscopic section shows an organizing hemorrhagic pericarditis (*A*). There is no evidence of myocarditis in this section in which the myocardium (*C*) is separated from the pericardium by epicardial fat (*B*).

liver cells in the central portion of the hepatic lobules. The adrenal cortices, bilaterally, were atrophic.

Cultures of the pericardial exudate taken at the time of autopsy showed no growth. A guinea pig inoculated with this material and killed in two months showed no evidence of tuberculosis.

COMMENT

The difficulty in differentiating acute nonspecific pericarditis from acute myocardial infarction is shown quite clearly. Many of the classic features of myocardial infarction were present. The patient was in an older age group; the onset, location and radiation of pain were typical; fever and leukocytosis were present, and a friction rub developed. In retrospect it is seen that the significant points suggesting the presence of pericarditis were the relation of the pain in the chest to respiration, the constancy, duration and intensity of the friction rub and the failure of development of electrocardiographic changes suggesting myocardial infarction.

Postmortem examination unequivocally established the primary disease as being in the pericardium and showed intense hemorrhagic changes with an element of cardiac tamponade. In the reported cases of benign pericarditis in which pericardicentesis was performed, the large majority revealed hemorrhagic fluid. Nathan and Dathe [3] demonstrated hemorrhagic fluid in four of five cases. Porter and his associates [4] described serosanguineous fluid in each of four cases. Thus, it seems probable that in such instances anticoagulant therapy would intensify bleeding into the pericardial sac. The supposition that the above case terminated fatally in part owing to the anticoagulant therapy appears justifiable. Further reports of similar circumstances, which undoubtedly have occurred elsewhere, will be necessary to substantiate such an opinion.

CONCLUSIONS

A case of nonspecific pericarditis with a fatal termination is presented.

The probable harmful effect of anticoagulant therapy is considered.

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3. Nathan, D. A., and Dathe, R. A.: Pericarditis with Effusion Following Infections of the Upper Respiratory Tract, Am. Heart J. **31**:115, 1946.

4. Porter, W. B.; Clark, O., and Porter, R. R.: Nonspecific Benign Pericarditis, J. A. M. A. **144**:749 (Oct. 28) 1950.

Progress in Internal Medicine

HYPERTENSION AND HYPERTENSIVE CARDIOVASCULAR DISEASE

Review of Recent Observations

A. C. CORCORAN, M.D.
IRVINE H. PAGE, M.D.
G. M. C. MASSON, Ph.D.
ROBERT D. TAYLOR, M.D.
AND
HARRIET DUSTAN, M.D.
CLEVELAND

THE GREAT increase in the productive study of cardiovascular diseases generally and of hypertensive disease in particular has been especially notable in the period July 1949 to July 1950. The review which follows deviates from the staid and sometimes tedious paths of the classic review in that the field is considered in terms of concepts and technics with which we have some personal familiarity. Topics which could not readily fit into this frame have regretfully been omitted from consideration, while in order to maintain the perspective it has sometimes been necessary to extend beyond the time limits originally set. Lest this approach be considered unduly presumptuous, we note that it was selected at the request of the Chief Editor.

In a field which is changing so rapidly and in which the animal experiments of the recent past will almost surely soon be reflected in new approaches to clinical diagnosis and treatment, the inclusion of what may seem to some a disproportionate volume of purely experimental material seems to us justifiable. Experimental hypertensive vascular disease is considered under several major headings, first, the factors which elicit hypertension, and second, those which modify it, to which we add a third, a concept of pathogenesis. These considerations deal with renal and hormonal hypertension, since experimental neurogenic hypertension does not seem to justify consideration in a review at this time.

Clinical hypertension is considered under two major heads: (1) mechanisms and pathogenesis of the various forms of hypertension, with which we have included a discussion of arteriosclerosis that, for convenience, incorporates some experimental material, and (2) the treatment of essential vascular hypertension and of its major complications in the light of our recent experience and of present concepts of mechanism and management.

EXPERIMENTAL HYPERTENSION AND VASCULAR DISEASE

A. *Factors Eliciting Hypertension.*—Methods used in this laboratory for the establishment of hypertension in rats are (1) production of silk perinephritis, (2) administration of desoxycorticosterone acetate (DCA) and (3) treatment with

From the Research Division, Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute.

Dr. Dustan is a Postdoctorate Fellow, National Heart Institute, National Institutes of Health, United States Public Health Service.

suspensions of crude lyophilized anterior pituitary or extracts thereof. A comparison of results with these methods [1] indicates that renal hypertension and hypertension induced by desoxycorticosterone acetate are the most consistently reproducible and severe and that the latter type runs a predictable course. We have not as yet attempted two new procedures which have been described for the production of renal hypertension in rats. These are Rau's method of encapsulating the kidney in a shell formed by spraying on a solution of a plastic in a volatile solvent [2] and the application of an adjustable metal clamp to the renal artery.[3] The latter is in essence a micro-Goldblatt method and the former, like the procedure of Flasher, Drury and Sobin,[4] an adaptation of Abram and Sobin's method of causing perinephritis by fitting the kidney in a latex capsule.

Choline deficiency in weanling rats results in severe renal damage,[5] and Best and Hartroft [6] have reported that about one third of rats subjected to such deficiency and then given normal diets became hypertensive some months later. The hypertension is roughly proportionate to the degree of residual renal damage and scar. It is tempting to relate this hypertension to the increased arterial pressure sometimes observed in human beings under conditions of severe dietary deficiency. However, since the renal disease of choline deficiency probably has no human analog, such a comparison is probably unjustified. The closest human analog of this interesting phenomenon is the hypertension of chronic atrophic pyelonephritis. The process is also probably analogous to hypertension induced by subtotal renal infarction.

Chickens have been observed to respond to feeding with isotonic or hypertonic solutions of sodium chloride by hypertension.[7] Recently, rats given 1.5 to 2 per cent sodium chloride solutions have also been noted to display increased arterial pressure.[8] At the end of six weeks no renal lesions were seen in these animals, whereas such changes would have been expected in rats treated with desoxycorticosterone acetate and 1 per cent saline solution. It seems likely that the mechanisms of desoxycorticosterone-saline and hypertonic saline hypertension are similar, and that the principal difference is one of greater severity of the process

1. (*a*) Masson, G. M. C.; Corcoran, A. C., and Page, I. H.: Experimental Vascular Disease Due to Desoxycorticosterone Acetate and Anterior Pituitary Extract: I. Comparison of Functional Changes, J. Lab. & Clin. Med. **34**:1416, 1949. (*b*) Masson, G. M. C.; Hazard, J. B.; Corcoran, A. C., and Page, I. H.: Experimental Vascular Disease Due to Desoxycorticosterone and Anterior Pituitary Factors: II. Comparison of Pathologic Changes, Arch. Path. **49**:641 (June) 1950.

2. Rau, G. C.: Experimental Hypertension Produced by a Plastic Capsule Applied to the Kidney, Science **111**:229, 1950.

3. Munnell, E. R., and Gregg, D. E.: A Small Adjustable Renal Artery Clamp for Production of Chronic Hypertension in the Rat, Proc. Soc. Exper. Biol. & Med. **73**:645, 1950.

4. Flasher, J.; Drury, D. R., and Sobin, S.: Persistent Unilateral Hypertension in the Rabbit, Am. J. Physiol. **158**:433, 1949.

5. Lalich, J. J.; Kline, B. E., and Rusch, H. P.: Degenerative Renal Lesions Induced by Prolonged Choline Deficiency, Arch. Path. **48**:583 (Dec.) 1949.

6. Best, C. H., and Hartroft, W. S.: Nutrition, Renal Lesions and Hypertension, Federation Proc. **8**:610, 1949.

7. Lenel, R.; Katz, L. N., and Rodbard, S.: Arterial Hypertension in the Chicken, Am. J. Physiol. **152**:557, 1948.

8. Sapirstein, L. A.; Brandt, W. L., and Drury, D. R.: Production of Hypertension in the Rat by Substituting Hypertonic Sodium Chloride Solutions for Drinking Water, Proc. Soc. Exper. Biol. & Med. **73**:82, 1950.

in animals given excess exogenous sodium-retaining steroid. In this view the nephrosclerotic activity of desoxycorticosterone acetate is incidental to its sodium-retaining property and is not a direct action of the steroid on vessel walls.

Grollman and Halpert [9] confirm earlier observations by showing that unilateral nephrectomy causes increased arterial pressure (150 mm. Hg) in about one-half the adult rats of their strain. Bilateral nephrectomy in rats causes hypertension in about two thirds of the cases.[10] Postnephrectomy hypertension is visualized as due to a loss of a renal incretory function which tends to maintain pressure at normal levels. Bilateral nephrectomy also elicits hypertension in dogs,[11] so that this phenomenon is not species specific.

On the other hand, use of desoxycorticosterone acetate causes at most only modest and transitory increases of pressure in dogs, in contrast to its action in the rat.[12] It seems likely that an explanation of this difference may be found in differences in renal mechanisms of sodium transfer as between the rat and the dog, a view consistent with the association of the pressor action of desoxycorticosterone acetate in human beings with renal and adrenal damage.

Spontaneous hypertension is rare in animals other than man. We have not been convinced of its occurrence in rats, as much because of the relative unreliability of most methods of measurement of pressure as because of wide fluctuations in pressure registrations. Stamler, Katz and Rodbard [13] have described spontaneous hypertension in dogs and defined it as a condition in which resting arterial pressure is greater than 185/100 mm. Hg. The renal plasma flow and glomerular filtration rate were normal in such animals, as was the filtration fraction, while serial renal clearances showed no tendency toward progressive impairment of renal function over long periods. This might be taken as an indication that factors other than high blood pressure underlie progressive renal damage in hypertensive human beings. However, it is generally recognized that in the absence of the syndrome of malignant hypertension dogs are very resistant to progressive arterial disease.

Studies on the functional changes which are associated with experimental hypertension have begun to throw some light on its mechanisms. Braun-Menéndez and Covián [14] had found that the hypertension of bilaterally nephrectomized rats was associated with increases in blood and extracellular fluid volumes. Braun-Menéndez and Martinez [15] noted that similar abnormalities occur in rats with renal (perinephritic) hypertension and with hypertension due to administration of

9. Grollman, A., and Halpert, B.: Renal Lesions in Chronic Hypertension Induced by Unilateral Nephrectomy in the Rat, Proc. Soc. Exper. Biol. & Med. **71**:394, 1949.

10. Tobian, L., Jr.: Hypertension Following Bilateral Nephrectomy, J. Clin. Investigation **29**:849, 1950.

11. Grollman, A.; Muirhead, E. E., and Vanatta, J.: Role of the Kidney in Pathogenesis of Hypertension as Determined by a Study of the Effects of Bilateral Nephrectomy and Other Experimental Procedures on the Blood Pressure of the Dog, Am. J. Physiol. **157**:21, 1949.

12. Masson, G. M. C.; Page, I. H., and Corcoran, A. C.: Vascular Reactivity of Rats and Dogs Treated with Desoxycorticosterone Acetate, Proc. Soc. Exper. Biol. & Med. **73**:434, 1950.

13. Stamler, J.; Katz, L. N., and Rodbard, S.: Serial Renal Clearances in Dogs with Nephrogenic and Spontaneous Hypertension, J. Exper. Med. **90**:511, 1949.

14. Braun-Menéndez, E., and Covián, M. R.: Mecanismo de la hipertensión de las ratas totalmente nefrectomizadas, Rev. Soc. argent. de biol. **24**:130, 1948.

15. Braun-Menéndez, E., and Martinez, C.: Aumento del volumen sanguineo y del liquido extracelular en ratas diabéticas e hipertensas, Rev. Soc. argent. de biol. **25**:168, 1949.

desoxycorticosterone acetate. They also noted that high protein or high sodium feedings or diabetes induced by subtotal pancreatectomy favors the production of hypertension in rats; these "sensitizing" conditions cause similar but smaller changes in fluid volume. Confirmatory to a degree is the observation [16] that the water content of the heart is increased in renal hypertension, a fact which argues against acceptance of wet heart weights as evidence of true hypertrophy. Highly significant are recent findings [17] that early in renal hypertension rats show no definite changes in the tissue water but that later on there occur an increase in water and sodium and a decrease in potassium. Interestingly, hypothalamic lesions can elicit comparable changes in tissue water and electrolytes,[18] although unfortunately arterial pressure was not measured in the latter experiments.

The genesis of experimental hypertensive cardiovascular disease is gradually becoming resolved. Krakower and Heino [19] have demonstrated by giving hypertonic saline solution to chickens for only nine hours that cardiac hypertrophy of substantial degree occurs within 24 hours; it is associated with an increase in muscle mass and, presumably, in intracellular water. The inference is that cardiac hypertrophy must be considered as an immediate response of the heart to increased energy output. In renal hypertensive rats Rather [20] has shown that one half of the ultimate increase in heart weight is reached in about 10 days and that adrenalectomy prevents this hypertrophy, presumably because it decreases arterial pressure and induces sodium loss.

Byrom and Dodson [21] seem to have shown that increased arterial pressure is the major determinant of hypertensive vascular disease; others have at times suggested other factors, notably hypothetical toxic renal secretions. However, Muirhead, Vanatta and Grollman [22] have demonstrated that the kidney need not be concerned in vascular lesions, since these appear in dogs after bilateral nephrectomy. In this species the lesions are often associated with necrotic foci, generally in smooth muscle.

Although in rats the initiating mechanisms of hypertension from perinephritis and from administration of desoxycorticosterone acetate and preparations of the anterior lobe of the pituitary seemed to us in each case different, we were impressed [1b] by the similarity of the resultant vascular diseases. In each case the renal lesions correspond precisely with those of malignant hypertension in human beings. Although the lesions in mesenteric and hepatic arteries have been described

16. Olsen, N. S.: Chemical Changes in Experimental Renal Hypertension, Am. J. Physiol. **161**:448, 1950.

17. Laramore, D. C., and Grollman, A.: Water and Electrolyte Content of Tissues in Normal and Hypertensive Rats, Am. J. Physiol. **161**:278, 1950.

18. Stevenson, J. A. F.; Welt, L. G., and Orloff, J.: Abnormalities of Water and Electrolyte Metabolism in Rats with Hypothalamic Lesions, Am. J. Physiol. **161**:35, 1950.

19. Krakower, C. A., and Heino, H. E.: Cardiac Hypertrophy, Arch. Path. **47**:475 (May) 1949.

20. Rather, L. J.: Experimental Cardiac Hypertrophy: Rate of Development and Effects of Adrenalectomy, Am. J. Physiol. **159**:153, 1949.

21. Byrom, F. B., and Dodson, L. F.: The Causation of Acute Arterial Necrosis in Hypertensive Disease, J. Path. & Bact. **60**:357, 1948.

22. Muirhead, E. E.; Vanatta, J., and Grollman, A.: Hypertensive Cardiovascular Disease: An Experimental Study of Tissue Changes in Bilaterally Nephrectomized Dogs, Arch. Path. **48**:234 (Sept.) 1949.

as the equivalents of periarteritis nodosa in human beings, they were not so considered by us. Rather, on the principle of diagnostic economy, they were interpreted as the species-specific expressions of hypertensive vascular disease in the splanchnic vessels of the rat. The concurrent cerebral lesions of encephalomalacia and the focal bleeding were due to segmental necrosis of small vessels. The associated capillary changes are reminiscent of those described by Scheinker [23] in hypertensive cerebrovascular disease in human beings. Cerebral lesions induced by desoxycorticosterone acetate overdosage in rats have been considered in more detail by others.[24]

Parenchymatous and renal vascular lesions were noted by us,[1b] as by others,[25] to follow rather than precede the onset of hypertension, observations which are in accord with the view that hypertensive vascular disease is in large measure a result of arterial hypertension as such.

B. *Factors Modifying Hypertension.*—The course of experimental hypertension can be modified by changes in dietary and hormonal environments and, in the case of renal hypertension, by removal of the offending kidney.

Dietary influences consist in changes in electrolyte and protein content. As noted above, chickens and rats both acquire hypertension when placed on diets which provide large excesses of sodium, and provision of excess sodium is generally recognized as essential to the establishment of desoxycorticosterone hypertension in rats. Indeed, desoxycorticosterone acetate is nontoxic when given in otherwise lethal doses to rats on sodium and chloride-free diets.[26] Sodium excess in rats also potentiates hypertension due to perinephritis and reduces survival in such animals.[27] Postnephrectomy hypertension is dependent on the provision of salt.[10] However, in dogs with renal hypertension, sodium restriction does not significantly decrease arterial pressure nor does sodium excess augment it,[28] a fact which corresponds with the disparate effects of desoxycorticosterone acetate in these two species.

With regard to protein, high protein diets increase pressure in renal hypertensive rats [27b, c] and are essential to the hypertension induced by injection of lyophilized anterior pituitary.[29] While protein hydrolysates substitute for protein in mainte-

23. Scheinker, I. M.: Hypertensive Cerebral Swelling: A Characteristic Clinicopathologic Syndrome, Ann. Int. Med. **28**:630, 1948.

24. Timiras, P. S.; Faribault, C., and Selye, H.: The Age Factor in the Brain Lesions Produced by Desoxycorticosterone Overdosage, Geriatrics **4**:225, 1949.

25. Friedman, S. M.; Polley, J. R., and Friedman, C. L.: The Effect of Desoxycorticosterone Acetate on Blood Pressure, Renal Function and Electrolyte Pattern in the Intact Rat, J. Exper. Med. **87**:329, 1948.

26. Selye, H.; Stone, H.; Timiras, P. S., and Schaffenburg, C.: Influence of Sodium Chloride upon the Actions of Desoxycorticosterone Acetate, Am. Heart J. **37**:1009, 1949.

27. (*a*) Danford, H. G., and Herrin, R. C.: Some Physiological Effects of Restricted Salt Diet in Hypertensive and Normal Rats, Am. J. Physiol. **159**:566, 1949. (*b*) Braun-Menéndez, E., and Martinez, C.: Mayor frecuencia de hipertensión por perinefritis o desoxicorticosterona en ratas diabéticas, Rev. Soc. argent. de biol. **25**:162, 1949. (*c*) Handler, P., and Bernheim, F.: Importance of Dietary Protein, Calories and Salt in Experimental Renal Hypertension, Am. J. Physiol. **160**:31, 1950.

28. Page, I. H., and Lewis, L. A.: Influence of Protein, Carbohydrate and Salt on Arterial Pressure of Dogs with Experimental Renal Hypertension, Am. J. Physiol. **156**:422, 1949.

29. de Grandpré, R.; Dontigny, P., and Leduc, J.: Influence des hydrolysats de proteines sur la production de nephrosclérose et d'hypertension par des préparations de lobes antérieurs d'hypophyse, Rev. canad. de biol. **9**:100, 1950.

nance of pituitary hypertension, urea, tyrosine and phenylalanine are not necessary to renal hypertension.[27e] Restriction of calories to an amount just sufficient for growth decreases arterial pressure in renal hypertensive rats, possibly because of a lack of the nitrogen-sparing action of caloric excess. Bearing on the problem of the rice diet is the fact that sodium restriction has little effect on pressure in rats with renal hypertension fed high protein rations, although sodium excess raises pressure when given to hypertensive rats on low protein diet.[27e]

Handler and Bernheim [30] found that the use of pituitary adrenocorticotropic hormone (ACTH) restores hypertension in hypertensive rats placed on low protein diets, but that it has no additive effect on the elevated blood pressure of those fed diets rich in protein. They suggest that the hypotensive effect of protein restriction may be due to relative deficiency in the formation of ACTH. The same authors [31] have confirmed the production of hypertension in rats as a late sequel to acute choline deficiency and have repeated their observations on the depressor effects of low protein and low sodium diets and on the pressor effect of diets which are rich in either or both of these constituents. In considering their demonstrations, particularly with regard to the effect of protein feeding, it is perhaps well to bear in mind that the conditions of their experiments were such as to have caused relatively severe renal damage.

Just as ACTH administration increases arterial pressure in renal hypertensive rats, so use of cortisone elicits hypertension in rats with experimental serum nephritis,[32] and its pressor activity is more pronounced in rats which have been adrenalectomized before treatment with nephrotoxic serum and cortisone. The pressor effect of cortisone in these nephritic rats contrasts somewhat with its effects and those of ACTH in human glomerulonephritis.[33] The pressor effect observed corresponds with the sensitization to the pressor action of desoxycorticosterone observed in the presence of renal damage, clinical or experimental, and also after adrenalectomy or in Addison's disease. However, ACTH and adrenal cortex extract both inhibit the vascular lesions caused by desoxycorticosterone acetate in rats. While blood pressure was not measured, the inhibition of cardiac hypertrophy by adrenal cortex extracts would suggest that hypertension was also prevented.[34]

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30. Handler, P., and Bernheim, F.: Physiological Basis for Effects of Low-Protein Diets on Blood Pressure of Subtotally Nephrectomized Rats, Am. J. Physiol. **162**:368, 1950; Effect of Choline Deficiency on ACTH Production and on Hypertension of Subtotally Nephrectomized Rats, ibid. **162**:375, 1950; Diminished ACTH Production in Rats on Low Protein Diets: Explanation of Relationship Between Dietary Protein and Renal Hypertension, Federation Proc. **9**:399, 1950.

31. Handler, P., and Bernheim, F.: Influence of Dietary Factors on Hypertension Induced by Choline Deficiency, Am. J. Physiol. **162**:189, 1950.

32. Knowlton, A. I.; Loeb, E. N.; Stoerk, H. C., and Seegal, B. C.: The Development of Hypertension and Nephritis in Normal and Adrenalectomized Rats Treated with Cortisone, Proc. Soc. Exper. Biol. & Med. **72**:722, 1949.

33. Farnsworth, E. B.: Acute and Subacute Glomerulonephritis Modified by Adrenocorticotropin, Proc. Soc. Exper. Biol. & Med. **74**:57, 1950. Thorn, G. W.; Merrill, J. P.; Smith, S.; Roche, M., and Frawley, T. F.: Clinical Studies with ACTH and Cortisone in Renal Disease, Arch. Int. Med. **86**:319 (Sept.) 1950.

34. Woodbury, D. M.; Rosenberg, C. A., and Sayers, G.: Antagonism of Adrenotrophic Hormone (ACTH) and Adrenal Cortical Extract (ACE) to Desoxycorticosterone (DCA): Pathological Changes, Federation Proc. **9**:139, 1950.

Using a nephrotoxic serum which elicited both nephritis and mild hypertension, Knowlton and her co-workers [35] report that the pressure is not affected by administration of sodium chloride but that administration of desoxycorticosterone acetate results in a rapid rise of pressure to levels of 200 mm. Hg and that withdrawal of desoxycorticosterone treatment at the end of a few weeks results in recession of the hypertension in some of the animals. Somewhat similarly, Braun-Menéndez,[27b] Gross [36] and we [1b] have found that doses of desoxycorticosterone acetate which are in themselves insufficient to elicit hypertension in normal or in unilaterally nephrectomized rats do cause an increase of arterial pressure in rats with mild hypertension due to unilateral perinephritis.

Hypertension due to administration of desoxycorticosterone acetate which has been present for 28 days persists after withdrawal of treatment with the substance in four of seven rats,[37] much as does the hypertension caused by combined nephritis and desoxycorticosterone administration.[35] Persistent desoxycorticosterone hypertension cannot be attributed to concurrent morphological changes, a dissociation we have also observed in similar experiments. From a theoretical point of view, the persistence of desoxycorticosterone hypertension in some animals after withdrawal of treatment with the drug suggests that the continuing hypertension is due to a mechanism other than desoxycorticosterone excess.

Selye [38] reports that desoxocortisone (17-hydroxy-desoxycorticosterone; Reichstein's compound S) in doses of 2.5 mg. daily causes a syndrome of hypertension and nephrosclerosis identical with that obtained with desoxycorticosterone acetate. However, using pellet implants, but otherwise under similar experimental conditions, we [39] were unable to demonstrate such changes. The disparate observations require further study, since desoxocortisone may be one of the naturally occurring adrenal hormones with salt-retaining activity.

It has long been recognized that hypophysectomy or adrenalectomy interferes with the development of or causes remission in experimental renal hypertension. The mechanism of this change is obscure, although as shown by Lewis and Page (unpublished data) relatively small doses of adrenal hormone materials can restore hypertension in renal hypertensive dogs bilaterally adrenalectomized. However, adrenalectomy does not prevent hypertension induced in rats by excess sodium,[40] a fact which suggests that the adrenal gland acts largely through its effect on renal mechanisms of electrolyte metabolism. In agreement with this are Tobian's findings [10] that in rats use of desoxycorticosterone acetate does not further increase pressure after bilateral nephrectomy. In contrast is his finding that postnephrec-

35. Knowlton, A. I.; Loeb, A. N.; Seegal, B. C., and Stoerk, H. C.: Desoxycorticosterone Acetate: Studies on the Reversibility of Its Effect on Blood Pressure and Renal Damage in Rats, Endocrinology **45**:435, 1949.

36. Gross, F.: Die Wirkung von Desoxycorticosteronacetät und Kochsalz auf den experimentellen Hochdruck der Ratte, Arch. internat. de pharmacodyn. et de thérap. **81**:211, 1950.

37. Friedman, S. M., and Friedman, C. L.: Self-Sustained Hypertension in the Albino Rat: A Hypothesis to Explain It, Canad. M. A. J. **61**:596, 1949.

38. Selye, H.: Production of Hypertension and Hyalinosis by Desoxycorticosterone, Brit. M. J. **1**:203, 1950.

39. Masson, G. M. C.; Corcoran, A. C., and Page, I. H.: Comparative Activities of 17-Hydroxy-11-Desoxycorticosterone and 11-Desoxycorticosterone, Endocrinology **46**:441, 1950.

40. Sapirstein, L. A.; Brandt, W., and Drury, D. R.: Effect of Adrenalectomy on "Salt" Hypertension, Federation Proc. **9**:112, 1950.

tomy hypertension is prevented by adrenalectomy; however, the combination of nephrectomy and adrenalectomy may result in metabolic abnormalities incompatible with the development of hypertension.

Removal of a kidney which is causing hypertension by either arterial compression or perinephritis has long been recognized as resulting in remission of hypertension in dogs and, depending on the duration of hypertension, in rats. The regularity of remission in dogs and its irregularity in rats are attributed to the tendency of the latter species to have hypertensive vascular disease in the "normal" kidney. In rabbits Flasher and Drury [41] found that removal of a perinephritic kidney results in a slow decline of pressure to normal levels. Hypertension had not been present in these animals for more than two months, and it is possible that a longer duration of hypertension might have led to irreversible hypertension such as commonly occurs in renal hypertensive rats or in rats made hypertensive with desoxycorticosterone acetate. The renal origin of the residual postnephrectomy hypertension has recently been established by Byrom and Dodson [42] in rats with a renal arterial clamp on one kidney. Removal of the arterial compression accompanied with contralateral nephrectomy resulted in rapid return to normal of the arterial pressure and symptomatic improvement. At autopsy, the kidney was normal and healing lesions of hypertensive vascular disease were observed in the heart and the pancreas. Since the clamp must have protected the kidney from the hypertension, these authors have thus further substantiated the hypothesis that hypertension itself is a prime cause of hypertensive vascular disease.

Unilaterally nephrectomized rats made hypertensive by treatment with desoxycorticosterone acetate show an increase of arterial pressure when the remaining kidney is removed.[43] Similarly, the increased arterial pressure consequent on unilateral nephrectomy can be explained by supposing that the kidney causes hypertension in perhaps three different ways: 1. Hypertension results from the complete suppression of renal function, as by nephrectomy. 2. Hypertension may also result from some change in blood flow consequent on clamping of renal arteries or perinephritis (so-called Goldblatt or renal hypertension). 3. From the point of view of the effects of desoxycorticosterone acetate and of cortisone and salt, hypertension may occur indirectly from increased renal retention of sodium. Preliminary observations suggest that partial occlusion of the hepatic artery and portal vein causes some decrease in arterial pressure in renal hypertensive dogs.[44] Further studies are necessary first to substantiate the finding and to elucidate the mechanism.

C. *Pathogenesis of Experimental Hypertension.*—Our analysis of the genesis of renal hypertension, however, does not establish its mechanisms, except to suggest that they are varied. The renal pressor system (renin, angiotonin or hypertensin, renin substrate or hypertensinogen) is also most certainly one of these, but its precise

41. Flasher, J., and Drury, D. R.: Effects of Removal of the Ischemic Kidney in Rabbits with Unilateral Renal Hypertension as Compared to Unilateral Nephrectomy in Normal Rabbits, Am. J. Physiol. **158**:438, 1949.

42. Byrom, F. B., and Dodson, L. F.: The Mechanism of the Vicious Circle in Chronic Hypertension, Clin. Sc. **8**:1, 1949.

43. Hall, C. E., and Hall, O.: Persistence of Desoxycorticosterone Induced Hypertension in the Nephrectomized Rat, Proc. Soc. Exper. Biol. & Med. **71**:690, 1949.

44. Davis, L.; Tanturi, C., and Tarkington, J.: The Effect of Reduced Blood Flow to the Liver in Renal Hypertension, Surg., Gynec. & Obst. **89**:360, 1949.

participation is entirely controversial. Some of the controversy stems from the fact that none of the components of the system has yet been definitely isolated in chemically pure form, so that the word "renin" means in fact an appropriate renal extract, "renin substrate" (hypertensinogen), a suitable preparation from plasma protein, and "angiotonin" (hypertensin), a mixture of polypeptides. The nature of the "sustained pressor principle" is still under study.[45]

New properties of renin have been described, notably that it causes diuresis and sodium loss which outlast its pressor activity in rabbits [46] and that it causes a prolonged proteinuria in rats.[47] The proteinuria is abolished by adrenalectomy and restored by treatment with cortisone, desoxycorticosterone acetate or adrenal cortex extract.[48]

That renal vasomotor influences may affect renin seems likely on two counts. First, stimulation of the frontal lobe in cats causes increased arterial pressure and decreased renal volume due to renal ischemia; repeated stimulations increase basal blood pressure of the animals and result in the appearance in the blood of detectable amounts of renin.[49] Similarly, renal denervation tends to decrease the renin content of the normal dog kidney.[50] Traumatic shock increases, first, the renin content of renal venous blood and, later, the renin content of the kidney, but neither phenomenon is observed when the kidneys are denervated.[51] The increase in renin content in shock is presumably the result of severe ischemia, since complete or partial occlusion of the renal artery also increases renin content.[52] Using a method based on the formation of angiotonin,[53] the same authors showed that renin is either produced or stored in the subcapsular zone of the renal cortex.[54]

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45. Helmer, O. M., in Conference on Factors Regulating Blood Pressure, Jan. 8 and 9, 1948, New York, Josiah Macy, Jr., Foundation, 1948; ibid., Feb. 23 and 24, 1950.

46. Hughes-Jones, I. C.; Pickering, G. W.; Sanderson, L. H.; Scarborough, H., and Vandenbroucke, J.: The Nature of the Action of Renin and Hypertensin on Renal Function in the Rabbit, J. Physiol. **109**:278, 1949.

47. Addis, T.; Barrett, E.; Boyd, R. L., and Ureen, H. J.: Renin Proteinuria in the Rat, J. Exper. Med. **89**:131, 1949.

48. Addis, T., and Boyd, R. L.: Adrenalectomy and Renin Proteinuria in the Rat, Federation Proc. **8**:1, 1949. Addis, T.; Marmoston, J.; Goodman, H. C.; Sellers, A. L., and Smith, M.: Effect of Adrenalectomy on Spontaneous and Induced Proteinuria in the Rat, Proc. Soc. Exper. Biol. & Med. **74**:43, 1950.

49. Langford, H. G.; Vester, J. W., and Hoff, E. C.: Effect of Electrical Stimulation of the Frontal Cortex upon the Production of Renin by the Kidneys, Am. J. Med. **8**:394, 1950.

50. Introzzi, A. S.; Manrique, J.; Raffaele, T., and O'Farrel, M. I.: Efecto de la desnervación renal sobre el contenido de renina en la capa cortical del riñón, Rev. Soc. argent. de biol. **25**:16, 1949.

51. Introzzi, A. S.; Manrique, J.; Raffaele, T.; O'Farrel, M. I., and Desgens, C.: Estudios sobre la renina en el "shock" traumático experimental: II. Efecto del shock traumático experimental sobre la renina de la capa cortical del riñón y de la sangre, Medicina, Buenos Aires **10**:1, 1950; III. Influencia de la desnervación renal sobre el efecto del "shock" traumático experimental en el contenido de renina en la cortical del riñón y en la sangre, ibid. **10**:101, 1950.

52. Taquini, A. C., and Fasciolo, J. C.: Acción de la isquemia incompleta sobre el contenido de renina del riñón, Medicina, Buenos Aires **9**:111, 1949. Fasciolo, J. C., and Taquini, A. C.: Isquemia renal completa y contenido de renina renal, ibid. **9**:107, 1949.

53. Fasciolo, J. C., and Taquini, A. C.: Un método para la estimación de la renina en los tejidos, Medicina, Buenos Aires **9**:117, 1949.

54. Taquini, A. C.; Fasciolo, J. C., and Fernández Luna, D.: El lugar de formación de la renina dentro del riñón, Medicina, Buenos Aires **10**:174, 1950. Fasciolo, J. C.: The Renin Content of Kidney, Acta physiol. Latino Americana **1**:7, 1950.

Participation of renin in renal hypertension continues to be suggested by observations which indicate that "antirenin" relieves renal hypertension in dogs.[55] That a sufficient residue of normal renal tissue is essential to renal hypertension is borne out by the observation that prolonged periods of total renal ischemia interfere with the later establishment of renal hypertension by arterial compression.[56]

Discontinuous intravenous injections of renin in rabbits (seven daily doses) do not cause a sustained increase in arterial pressure.[57] The same is probably true of daily subcutaneous injections of renin in rats,[58] although animals thus treated showed a cachexia reminiscent of the wasting which occurs in malignant hypertension. Indeed, failure of prolonged treatment with renin to cause sustained hypertension has long been advanced against its participation in renal hypertension. However, quite recently Sobin has informed us that he induced long-lasting increases of arterial pressure in rabbits by suitably adjusted infusions of renin.

The status of the VEM-VDM (vasoexcitor material–vasodepressor material) system is considered below. Of particular interest is the view that estimates of VDM indicate that it does not enter into the mechanism of hypertension owing to desoxycorticosterone acetate, although it does show alterations in renal hypertension in rats.[59]

The classic clinical hypertension of adrenal origin is that of Cushing's syndrome, and it is generally assumed that desoxycorticosterone hypertension is its experimental analog. Since one of the major actions of desoxycorticosterone acetate is sodium retention, and since sodium is essential in desoxycorticosterone hypertension, it also seems likely that desoxycorticosterone hypertension is in fact sodium hypertension. Thus, rats and chickens display hypertension after administration of salt or desoxycorticosterone acetate and the rat exhibits it most effectively when both are combined. Under appropriate conditions cortisone has a desoxycorticosterone-like action in the rat, as desoxocortisone may also have. Desoxycorticosterone acetate does not increase arterial pressure after nephrectomy, and it is our working hypothesis that its principal action is mediated through renal retention of sodium. The hypertension which occurs in dogs and rats after bilateral nephrectomy is also apparently dependent on sodium intake. It, therefore, seems likely that sodium retention is a pressor mechanism common to postnephrectomy hypertension and to the hypertension induced by administration of desoxycorticosterone and excess dietary sodium.

Other mechanisms of desoxycorticosterone activity have been suggested, such as the earlier observations that it tended to maintain circulating renin substrate in adrenalectomized animals. A more recent claim is that pressor responsiveness to

55. Kiely, J. P.; Kiely, J. M.; Osgood, B. G.; Marshall, J., and Wakerlin, G. E.: Further Studies on Prophylaxis and Therapeusis of Experimental Renal Hypertension with Renal Extracts, Federation Proc. **9**:70, 1950.

56. Hawthorne, E. W.: Experimental Renal Hypertension in the Dog Following Renal Ischemia, Proc. Soc. Exper. Biol. & Med. **73**:353, 1950.

57. Strehler, E., and Suter, E.: Zur Frage des Dauerhochdrucks nach Renininjektionen, Ztschr. f. d. ges. exper. Med. **115**:436, 1950.

58. Masson, G. M. C.; Corcoran, A. C., and Page, I. H.: Some Effects of Chronic Treatment of Rats with Renin, Am. J. Physiol. **162**:379, 1950.

59. Zweifach, B. W., and Shorr, E.: Desoxycorticosterone Hypertension in Relation to Hepatorenal Mechanisms, Federation Proc. **9**:141, 1950.

epinephrine and angiotonin is increased in desoxycorticosterone-hypertensive rats,[60] an observation which we have not been able to confirm.[12] Furthermore, Silva and Croxatto could not demonstrate in rats any increased vascular response to epinephrine and angiotonin specifically due to desoxycorticosterone acetate given intravenously.[61] Not bearing directly on the adrenal gland, but on pressor responsiveness in hypertension, are the observations [62] that rats with renal hypertension show increased responsiveness to arterenol and epinephrine, normal responses to phenylethylamine and tyramine and decreased response to isoamylamine. The wide variability of pressor responsiveness in animals [63] makes us cautious in accepting most such reported differences. However, as demonstrated by Moss and Wakerlin,[64] and in this laboratory (unpublished data), there are profound differences in the responses of dogs with renal hypertension and those with neurogenic (vasodepressor nerve section) hypertension to drugs such as tetraethylammonium chloride. The decrease of blood pressure caused by use of tetraethylammonium chloride, and also of dibenamine,® in the neurogenic hypertensive dog points definitely to the primacy of vasomotor nerves in the pressure elevation of this animal. Available data indicate that vasomotor control is substantially normal in renal hypertension.

In summarizing the above literature on experimental hypertension, we have attempted to place it in its usual perspective, separating the renal and adrenal mechanisms and influences. However, we have been influenced throughout by a concept of renal hypertension which would tend to unify these two mechanisms.[65] The views of others tend similarly. Thus, Grollman [11] has always sustained the view that renal hypertension was due to a lack of some renal antihypertensive factor (defined as an antipressor incretory function) rather than to an increased activity of any renal pressor agent, including the renal pressor system. Friedman and Friedman [37] have proposed a view that hypertension "may be expected to arise whenever the balance between the production of an adrenal D. C. A.-like pressor material and its handling by the kidney is interfered with," the assumption being that desoxycorticosterone acetate is inherently pressor. Rather,[66] who argues from the over-all adrenal enlargement found in renal hypertensive rats, suggests adrenal participation in renal hypertension.

60. Guillemin, R., and Selye, H.: Action des minéralo-corticoïdes sur le comportement du rein envers les substances vasopressives type angiotonine, Rev. canad. de biol. **9**:309, 1950.

61. Silva, V., and Croxatto, H.: Administración de desoxicorticosterona y sensibilidad a la hipertensina y adrenalina en ratas, Acta physiol. latino americana **1**:46, 1950.

62. Olsen, N. S.; Schroeder, H. A., and Menhard, E. M.: Effect of Certain Amines on the Blood Pressure of Normotensive and Hypertensive Rats, Proc. Soc. Exper. Biol. & Med. **74**:581, 1950.

63. Page, I. H., and Taylor, R. D.: Variations of Vascular Reactivity in Normal and Hypertensive Dogs, Am. J. Physiol. **156**:412, 1949.

64. Moss, W. G., and Wakerlin, G. E.: Role of the Nervous System in Experimental Renal Hypertension, Am. J. Physiol. **161**:435, 1950.

65. Masson, G.; Corcoran, A. C., and Page, I. H.: A Unifying Concept of the Pathogenesis of Experimental Hypertension, read before the International Congress of Cardiology, Paris, France, Sept. 3 to 5, 1950.

66. Rather, L. J.: The Pathogenesis of Hypertension Induced by Renal Constriction, J. Exper. Med. **92**:59, 1950; The Adrenals and Experimental Constrictive Renal Hypertension, Stanford M. Bull. **8**:119, 1950.

Our view is based on somewhat different evidence. First, it was noted that renal hypertensive rats or rats treated with renin show hypertrophy of the zona glomerulosa of the adrenal gland, which zone is considered to be the site of origin of the desoxycorticosterone-like corticosteroids. It was recalled that Olson and Deane [67] had shown glomerulosal hypertrophy as part of the change in acute choline disease in weanling rats. With these facts in mind, the natriuretic effect of renin was considered and the concept developed that renal hypertension may proceed in two phases. The first is associated with increased liberation of renin and activity of the renal pressor system which leads to sodium loss. In the second phase the adrenal glands tend to regulate this homeostatically by increased secretion of desoxycorticoids, and thus there is developed a vicious cycle of renal-adrenal pressor activity (fig.). This would account for the changes in tissue water noted

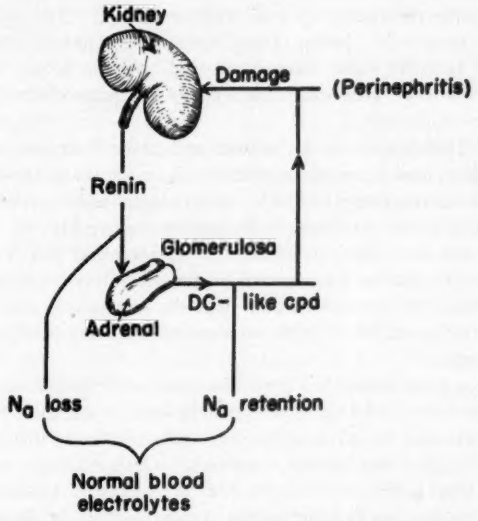

Diagram of renal-adrenal relationship in hypertension. *DC-like cpd.* refers to a desoxycorticosterone-like compound.

by Braun-Menéndez [15] and by Laramore and Grollman [17]; it would reconcile many existing inadequacies of current theories and would explain the self-sustaining tendencies of renal and desoxycorticosterone hypertensive disease.

CLINICAL HYPERTENSION

We have found it helpful to classify the various forms of hypertensive disease by cause or, when the cause is obscure, by description. Such classification facilitates diagnosis and, as will be shown, serves as a guide in treatment. Thus considered, there are two broad groups of hypertensive diseases: (1) hypertensions of known or attributable origin and (2) hypertensions of unknown origin.

67. Olson, R. E., and Deane, H. W.: A Physiological and Cytochemical Study of the Kidney and the Adrenal Cortex During Acute Choline Deficiency in Weanling Rats, J. Nutrition **39**:31, 1949.

Our present knowledge of the hypertensions of attributable origin derives in part from clinical observations and in almost equal degree from experiments such as those reviewed above. Laboratory tests have in every instance been inspired by nature's experiment, a clinical syndrome.

Renal Hypertension.—The renal pressor system (renin, renin substrate or hypertensinogen, angiotonin or hypertensin) remains as the presumptive initiating mechanism of renal hypertension, clinical and experimental. However, little progress has yet been made in the tedious task of isolating any of its components in definitively pure form, and, until this has been accomplished, it is obvious that our knowledge of the exact mechanism of renal hypertension must remain woefully incomplete. The probability that the renal pressor system may act on other systems, notably those arising in the adrenal gland, is mentioned above. What may be an important step toward the isolation of angiotonin is the separation of concentrates of angiotonin by the chromatography of crude mixtures.[68] The separation is done in a paper pulp column by elution of angiotonin with aqueous phenol. The yield is good, and the fact that many inactive materials seem to be left behind points to the possibility of a more satisfactory method for the quantitative determination of renin, as well as angiotonin.

The VEM-VDM hypothesis of Zweifach and Shorr [69] depends in part on their demonstration that, under certain conditions, such as renal anaerobiosis, kidney tissue will liberate a substance (VEM) which potentiates the action of epinephrine on the terminal vascular segments of the rat mesoappendix. However, VEM is still a phenomenon and not a substance. It is not clear that VEM activity as such can account for increased peripheral resistance, unless it can be supposed that its span of potentiation extends further than the metarterioles and to other substances than epinephrine, which, after all, cannot be incriminated in most forms of hypertensive diseases.

VDM, on the other hand, has been identified with ferritin and apoferritin [70]; the former is the ferric hydroxide-laden protein which constitutes the storage form of iron in the body, and the latter is the iron-depleted form of this protein. Ferritin has been shown to have antidiuretic properties,[71] which, although in our experience not profound, may have clinical relevance in conditions associated with water retention. Its participation in hypertension is still obscure. In chronic hypertension the peripheral blood gives a "neutral" reaction which is due to balanced excesses of both VEM and VDM. In our hands, ferritin—whatever it may do to the responsiveness of the metarterioles of the mesoappendix—has little or no effect on the normal or hypertensive rat's arterial pressure or pressor responsiveness to

68. Helmer, O. M.: A Simple Chromatographic Procedure for the Separation of Angiotonin from Crude Mixtures, Proc. Soc. Exper. Biol. & Med. **74**:642, 1950.

69. Zweifach, B. W., and Shorr, E.: Hepatorenal Vasotropic Factors in Blood of Patients with Essential Hypertension, in Conference on Factors Regulating Blood Pressure, Jan. 8 and 9, 1948, New York, Josiah Macy, Jr., Foundation.

70. Mazur, A., and Shorr, E.: Hepatorenal Factors in Circulatory Homeostasis: IX. The Identification of the Hepatic Vasodepressor Substance with Ferritin, J. Biol. Chem. **176**:771, 1948.

71. Baez, S.; Mazur, A., and Shorr, E.: Hepato-Renal Factors in Circulatory Homeostasis: XX. The Antidiuretic Action of Hepatic Vasodepressor, VDM (Ferritin), Am. J. Physiol. **162**:198, 1950.

epinephrine.[72] In reference to chronic congestive heart failure, Edelman and his co-workers [73] demonstrated the presence of renal ischemia in a group of patients. Increased renal extraction of oxygen was shown in increased arteriovenous difference, from 1.3 volumes per cent in control subjects to 3.5 volumes per cent in those in failure, with a calculated decrease in renal capillary oxygen tension. Thus, this low oxygen tension provides conditions in which VEM might well be formed, and, in fact, VEM was demonstrated in the renal venous blood of 10 of 12 patients in heart failure and in only three of 13 control subjects. Similarly, the hepatic venous blood had high titers of the vasodepressor, VDM, in 10 of 11 patients with cardiac disease and in only three of 14 controls.

Activation of the VEM-VDM system seems to be established, but, wisely, the authors concluded:

> In the present state of our knowledge it is not possible to define the relationship between the production of VEM by the ischemic, hypoxic kidney and the marked renal vasoconstriction in congestive heart failure.

Nor is the participation of the system any more obvious with regard to the many other physiological abnormalities which characterize cardiac failure, with the possible exception of oliguria.

With regard to ferritin, Hampton and Mayerson [74] propose for it still another role as the mechanism regulating the transfer of iron and iron-containing materials, such as hemoglobin, in the kidney, a function analogous to its action in the gastrointestinal tract. Interest in this arises particularly from their suggestion that when more iron is present than the renal ferritin-apoferritin system can transfer ferric hydroxide will form in the tubules and account for tubular necrosis in hemoglobinuric states.

Studies completed in 1942 have only recently been reported by Stock and Schroeder,[75] in which they accumulated evidence for the existence in the blood of 21 of 23 patients with hypertension of a substance which causes a prolonged increase of arterial pressure when injected into rats. The pressor activity did not occur in the majority of extracts from 22 normal persons. Its presence showed some correlation with the blood content of amines. Schroeder and Olsen [76] have called this material "pherentasin." It is characterized as a relatively unstable, nonprotein, amine-like material which is soluble in water, alcohol and chloroform, but not in purified benzin U. S. P., and recoverable in concentrations of 10 to 20 micrograms per liter of blood. It has been detected in the blood of 31 of 33 patients with renal hypertension and in only five of 18 patients with malignant hypertension. Smaller amounts were found in persons with "neurogenic" hypertension and in only one

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72. Corcoran, A. C.; Masson, G. M. C., and Schaffenburg, C.: Ferritin: Effect on Blood Pressure and Pressor Response in Rats, Federation Proc. **8**:28, 1949.

73. Edelman, I. S.; Zweifach, B. W.; Escher, D. J. W.; Grossman, J.; Mokotoff, R.; Weston, R. E.; Leiter, L., and Shorr, E.: Studies on VEM and VDM in Blood in Relation to Renal Hemodynamics and Renal Oxygen Extraction in Chronic Congestive Failure, J. Clin. Investigation **29**:925, 1950.

74. Hampton, J. K., and Mayerson, H. S.: Hemoglobin Iron as a Stimulus for the Production of Ferritin by the Kidney, Am. J. Physiol. **160**:1, 1950.

75. Stock, C. C., and Schroeder, H. A.: Pressor Substances in Arterial Hypertension: Activity and Amine Content of Crude Extracts of Blood, Am. J. Physiol. **160**:409, 1950.

76. Schroeder, H. A., and Olsen, N. S.: Pherentasin: A Pressor Substance Present in Arterial Hypertension, J. Clin. Investigation **29**:844, 1950.

of 14 patients with "endocrine hypertension." Its frequent occurrence in renal hypertension and in patients with advancing nephrosclerosis would seem to point to a renal origin or inactivation of the material. However, its frequent absence from blood in patients with malignant hypertension—most of whom show severe nephrosclerosis—leaves this point in doubt. It was detected in two of 26 normotensive controls; both of these had infectious mononucleosis. It is apparent that further studies will have to be done before "pherentasin" is added to the list of agents participating in the genesis of renal or other forms of hypertensive disease.

Although not directly concerned with hypertension, the chemistry of the vasoconstrictor which forms during clotting (serum vasoconstrictor or serotonin) has been clarified by Rapport,[77] who found that, as it is isolated from blood, it is a complex of equimolecular parts of creatinine and the sulfuric acid salt of an amine. The vasoactivity of serotonin, of course, cannot be attributed to the creatinine or the sulfate moieties, but to the residual part of the molecule, which seems to be 5-hydroxytryptamine. Its properties, such as instability and some of its solubilities, correspond fairly well with those of "pherentasin." Serotonin has less pressor than local vasoconstrictor activity, a fact which corresponds well with its presumed function of constricting a vessel firmly around a clot.

From the clinical aspect, Platt and Davson [78] contribute the conviction that they "are very reluctant to make a diagnosis of malignant hypertension [malignant phase of essential hypertension] in persons under 35 years of age or in any patient whose two parents are still living." Three patients are described who, with the use of this apothegm, were found, in fact, to suffer, respectively, from periarteritis nodosa, hydronephrosis and pheochromocytoma, although they presented the classic features of malignant hypertension. The authors' review of 188 cases of renal disease leads them to plead for a correct use of the term malignant hypertension. They suggest that, just as there is no meaning left in the term chronic interstitial nephritis, so the indiscriminate modern use of the term malignant hypertension to include almost any case of terminal hypertensive disease with renal failure is even less justifiable.

Platt and Davson found hypertension in 14 of their 26 cases of pyelonephritis and subscribe to the view that pyelonephritis is, in fact, a cause of hypertension, although the association is not obligatory. A similar point of view is that of Birchall and Alexander [79] in their summary of the medical aspects of pyelonephritis.

The association of hypertension with glomerulonephritis and the probability that such hypertension is of renal origin are generally recognized. Brod [80] has reviewed various aspects of acute glomerulonephritis in adult soldiers and emphasizes that the hypertension usually subsides within one or two months and that edema usually recedes at about the same time. The impairments of renal excretory functions (filtration rate, concentrating power, proteinuria) were remarkably per-

77. Rapport, M. M.: Serum Vasoconstrictor (Serotonin): V. The Presence of Creatinine in the Complex; A Proposed Structure of the Vasoconstrictor Principle, J. Biol. Chem. **180**:961, 1949.

78. Platt, R., and Davson, J.: A Clinical and Pathological Study of Renal Disease: II. Diseases Other Than Nephritis, Quart. J. Med. **19**:33, 1950.

79. Birchall, R., and Alexander, J. E.: Medical Aspects of Pyelonephritis, Medicine **29**:1, 1950.

80. Brod, J.: Acute Diffuse Glomerulonephritis, Am. J. Med. **7**:317, 1949.

sistent. He comes to the conclusion that hypertension and edema which persist for more than one month, irrespective of degree, are usually associated with a prolonged course and quite probably with ultimate progression into the chronic phase of the disease.

The mechanism of the toxemias of pregnancy is as obscure as ever, in spite of a spate of hypotheses. Stander's observation many years ago that the blood uric acid level is increased in the true later toxemias of pregnancy (preeclampsia and eclampsia) has been studied from a functional and diagnostic aspect by Chesley[81] and Chesley and Williams.[82] They found that the tendency to an increase in blood uric acid is attributable to two factors: (1) a decrease in the rate of glomerular filtration and (2) an increase in the tubular reabsorption of uric acid. Since hyperuricemia is not always present, they suggest that simultaneous determinations of the renal clearances of urea and uric acid will serve in the separation of preeclampsia from hypertensive disease and primary renal disease. Uncertainties remain concerning the mechanisms of excretion of uric acid. The probability is that most of it circulates bound to protein. Doubt persists about the specificity of the analytic methods in common use. Chesley emphasizes the combined test as a clinical tool rather than as a valid explanation of toxemic hyperuricemia.

Quite a different diagnostic criterion in toxemia is that suggested by Assali and collaborators.[83] They found that normal pregnant women show a decrease of arterial pressure following injection of tetraethylammonium chloride. This is somewhat lessened post partum. Neither before nor after delivery does Veratrum viride have much depressor effect. In contrast, women with eclamptogenic toxemia show a definite resistance to the depressor effect of tetraethylammonium chloride and a definite sensitivity to the depressor action of Veratrum. The differential disappears after delivery. Since we have included the hypertension of toxemic pregnancy with renal hypertension, it would be of interest to know whether or not patients with such conditions as acute glomerulonephritis resemble those with toxemia in their responses to tetraethylammonium chloride and Veratrum. However, it has been shown that the tetraethylammonium chloride "floor" (minimum pressure reached after rapid injection of the substance) rises during treatment with ACTH and sodium. It is known that sodium retention is one of the characteristics of toxemia and that adrenal cortex activity is increased during pregnancy.[84] From this it may follow that the heightened tetraethylammonium chloride floor in toxemia reflects sodium retention and does not bear directly on its basic mechanism.

Hypertensions of Cardiovascular Origin.—In this category the hypertensions due to coarctation of the aorta and to arteriosclerosis have much current interest.

81. Chesley, L. C.: Simultaneous Renal Clearance of Urea and Uric Acid in the Differential Diagnosis of the Late Toxemias, Am. J. Obst. & Gynec. **59**:960, 1950.

82. Chesley, L. C., and Williams, L. O.: Renal Glomerular and Tubular Function in Relation to the Hyperuricemia of Pre-Eclampsia and Eclampsia, Am. J. Obst. & Gynec. **50**:367, 1945.

83. Assali, N. S.; Brust, A.; Garber, S. T., and Ferris, E.: Comparative Study of Effects of TEAC and Veratrum Viride on Blood Pressure in Normal and Toxemic Pregnancies, J. Clin. Investigation **29**:290, 1950.

84. Ransohoff, W.; Brust, A. A.; Chambers, W. N.; Shapiro, A. P.; Reiser, M. D.; Loube, S. D.; Mirsky, I. A., and Ferris, E. B.: The Effect of Sodium Intake on the Action of ACTH in Uncomplicated Essential Hypertension, J. Clin. Investigation **29**:839, 1950.

The importance of a diagnosis of coarctation is greater than ever because of the prospects of successful operative cure. The major diagnostic criterion is, of course, the simple demonstration of relative hypotension in the legs. Björk and Liedholm [85] have studied the femoral pulse and have shown that a delayed peak in the curve can be pathognomonic of this condition. As concerns physical diagnostic methods, Wells and his associates [86] call attention to systolic and diastolic murmurs heard over the dorsal portion of the spine and the precordium. The dorsal vibrations are especially definite in phonocardiograms. Freeman and his coworkers [87] have done retrograde aortography by injection of 70 per cent iodopyracet (diodrast®) into the left common carotid. The technic was successful in 13 of 15 patients suspected of coarctation of the aorta and in nine of these visualized the exact location and degree of the narrowing; in four patients the aortographic findings contraindicated what might have been fruitless thoracotomy. Potts [88] has described operative technics and new instruments, and Gross [89] has published a monograph on the surgical treatment of congenital heart disease. Among 100 cases of coarctation he [90] found that operation relieved hypertension completely in 71 and partially in nine. There were 11 fatalities, seven of which now would be regarded as avoidable. He and others [91] describe the preparation of arterial grafts from frozen arterial segments which can be inserted in the area of resection.

The nature of hypertension in coarctation of the aorta is still a matter of debate. At first glance, it would seem logical that it should have the same mechanism as hypertension due to partial compression of a renal artery and, therefore, be of renal origin and, like renal hypertension, be associated with a generalized anteriolar constriction and increase in peripheral resistance throughout the body. With this view, Sealy and his associates [92] have ingeniously inserted lucite® grafts into the aorta above the renal arteries, which in effect produces coarctation. Their dogs had systolic and diastolic hypertension above and diastolic hypertension below the level of aortic narrowing. Renal blood flow was not decreased. Wang [93] reported a case in which narrowing of the aorta above the renal arteries as the result of arteriosclerosis resulted in severe hypertensive heart disease and death, and the presumption would be that the mechanism here also is that of renal hypertension. However, certain observations indicate that the mechanism of hypertension of coarctation may be much more mechanical and much less humoral-renal than has been supposed.

85. Björk, S., and Liedholm, K.: The Femoral Pulse Curve in Coarctation of the Aorta, Acta med. Scandinav. **136**:97, 1949.

86. Wells, B.; Rappaport, M., and Sprague, H.: The Graphic Registration of Basal Systolic Murmurs, Am. Heart J. **37**:586, 1949.

87. Freeman, N. E.; Miller, E. R.; Stephens, H. B., and Olner, M. B.: Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions: II. Coarctation of the Aorta, Ann. Int. Med. **32**:827, 1950.

88. Potts, W. J.: Technic of Resection of Coarctation of the Aorta with the Aid of New Instruments, Ann. Surg. **131**:449, 1950.

89. Gross, R. E.: Surgical Treatment for Abnormalities of the Heart and Great Vessels, Springfield, Ill., Charles C Thomas, Publisher, 1950.

90. Gross, R. E.: Coarctation of the Aorta: Surgical Treatment, Circulation **1**:41, 1950.

91. Gross, R. E.; Bill, A. H., Jr., and Pierce, E. C.: Methods for Preservation and Transplantation of Arterial Grafts, Surg., Gynec. & Obst. **88**:689, 1949.

92. Sealy, W. C.; DeMaria, W., and Harris, J.: Studies of the Development and Nature of Hypertension in Experimental Coarctation of the Aorta, Surg., Gynec. & Obst. **90**:193, 1950.

93. Wang, H.: Hypertension and Stenosis of the Abdominal Aorta, Cardiologia **15**:1, 1949.

These are the facts that (1) cerebral blood flow is increased in this condition and that cerebral vascular resistance is not; in essential hypertension cerebral blood flow is normal and resistance is increased [94]; (2) in coarctation the coronary blood flow is increased, as is the oxygen consumption of the heart; in hypertension coronary blood flow is normal.[95] Thus, it may be that the mechanical factors account for most of the hypertension and that renal mechanisms, if they operate at all, are not uniformly active or highly significant. However, this assumption suggests that the experimental and clinical hypertension observed after narrowing of the aorta just above the renal arteries is not an analog to coarctation at the arch but rather to the placing of a Goldblatt clamp proximal to the renal artery.

Hypertension due to aortic arteriosclerosis is only gradually becoming crystallized as an entity in the minds of busy clinicians. It is unfortunate that this common fluctuation and relatively benign process is not more accurately recognized. Too many patients find that their declining years are blighted by an unjustified diagnosis of essential or even of malignant hypertension when a little reflection should have led to the diagnosis of aortic arteriosclerosis. It is characterized by an increase in systolic arterial pressure, usually beginning about the age of 50, and is commoner in men than in women. The diastolic component is usually slight, and the variability of arterial pressure is great. The variability is due to wide differences in cardiac output. Cardiac output is increased greatly by effort or anxiety. In the person whose aorta has lost its elasticity, and therefore its *Windkessel* function, changes in output are reflected in corresponding fluctuations of systolic pressure. Also, the fact that pressure in these persons is a function of cardiac output has a further corollary: Rest, reassurance, mild sedation or any appropriate amulet or charm which will tend to decrease cardiac output will result in a decrease in arterial pressure. It can be assumed that most of the many useless drugs and regimens advocated for the control of essential hypertension derive from their ill considered use in patients with arteriosclerotic hypertension.

What may be considered a specific subgroup of cases of arteriosclerotic hypertension is made up of those in which intermittent claudication is associated with paroxysmal hypertension. These episodes are not related in severity to the degree of concurrent pain. That other than neural mechanisms participate is suggested by the fact that they are not completely relieved by treatment with tetraethylammonium chloride.[96]

The whole field of arterial disease is still semantically clouded by systems of nomenclature which outnumber their factual concepts. Moschcowitz's [97] definition of hyperplastic arteriosclerosis (intimal hyperplasia, splitting of the elastica interna and medial hypertrophy) as a necessary sequel to normal aging and normal intra-

94. Kety, S.: Circulation and Metabolism of the Brain, Am. J. Med. **8**:205, 1950.

95. Bing, R. J.; Hammond, M. M.; Handelsman, J. C.; Powers, S. R.; Spencer, F. C.; Eichenhoff, J. E.; Goodale, W. T.; Hafkenschiel, J. H., and Kety, S. S.: The Measurement of Coronary Blood Flow Oxygen Consumption and Efficiency of the Left Ventricle in Man, Am. Heart J. **38**:1, 1949.

96. Malinow, M. R.; Moja, B.; Otero, E., and Rosenbaum, M.: The Occurrence of Paroxysmal Hypertension in Patients with Intermittent Claudication, Am. Heart J. **38**:702, 1949.

97. Moschcowitz, E.: Hyperplastic Arteriosclerosis Versus Atherosclerosis, J. A. M. A. **143**:861 (July 8) 1950.

vascular tension provides at least a basis for study. He emphasizes, as do now many others, the distinction between such changes and those of atherosclerosis. Dock [98] views arteriosclerosis as occurring in four forms, only one of which—medial atrophy with fibrous replacement—can be viewed as a normal result of aging. The other three types are medial calcification, intimal thickening and fibrosis and atherosclerosis or atheroma. To this we would subscribe.

The complexity of the problem of atherosclerosis probably results from the concurrence in its pathogenesis of local lesions and of systemic and metabolic factors. As concerns the local lesions, Duguid[99] has posed the novel concept that intimal thickening is not in fact a productive overgrowth of tissue but rather the sequel of local thrombosis and deposition of fibrin. Paterson and Cottral[100] have drawn attention to the spontaneous medial lesions of chicks and the fact that these predispose to the localization of atheroma. Taylor and his co-workers[101] have shown that atherosclerotic deposits localize preferentially in rabbits at sites of medial damage, and they have described the sequence of aortic regeneration after local freezing. Similarly, in dogs aortic atheromas form at sites of injury by cauterization.[102] A comparison of aortic vascularization in various species shows that it is greatest in the dog and progressively less in human beings, chickens and rabbits[103]; this sequence suggests that greater aortic vascularity lessens the tendency to atherosclerosis. In this connection, Saphir and Gore[104] found lesions of small myocardial arteries characteristic of chronic rheumatic carditis in soldiers between 18 and 29 years of age who had died as a result of coronary atherosclerosis. They suggest that in some of the patients the large vessel lesions may have arisen at sites of healed inflammation which had disappeared into the atherosclerotic overlay.

As localizing factors in arteriosclerosis, Faber[105] draws attention to the sulfate-containing polyuronides and suggests that these carbohydrates may react with lipoproteins so that lipid is locally released in arterial walls.

But, as is suggested by a recent editorial review,[106] interest concentrates on systemic and not on local factors in atherogenesis and in particular on the participation of cholesterol. This is a natural result of the noteworthy experimental

98. Dock, W.: The Causes of Arteriosclerosis, Bull. New York Acad. Med. **26**:182, 1950.

99. Duguid, J. B.: Pathogenesis of Atherosclerosis, Lancet **2**:925, 1949.

100. Paterson, J. C., and Cottral, G. E.: Experimental Coronary Sclerosis: III. Lymphomatosis as a Cause of Coronary Sclerosis in Chickens, Arch. Path. **49**:699 (June) 1950.

101. Taylor, C. B.; Baldwin, D., and Hass, G. M.: Localized Arteriosclerotic Lesions Induced in the Aorta of the Juvenile Rabbit by Freezing, Arch. Path. **49**:623 (June) 1950.

102. Schlichter, J. A.; Katz, L. N., and Meyer, J.: The Occurrence of Atheromatous Lesions After Cauterization of the Aorta Followed by Cholesterol Administration, Am. J. M. Sc. **218**:603, 1949.

103. Schlichter, J., and Harris, R.: The Vascularization of the Aorta: II. A Comparative Study of Aortic Vascularization of Several Species in Health and Disease, Am. J. M. Sc. **218**:610, 1949.

104. Saphir, O., and Gore, I.: Evidence for Inflammatory Basis of Coronary Arteriosclerosis in the Young, Arch. Path. **49**:418 (April) 1950.

105. Faber, M.: The Human Aorta: Sulfate-Containing Polyuronides and the Deposition of Cholesterol, Arch. Path. **48**:342 (Oct.) 1949.

106. The Relation of Cholesterol to the Development of Atherosclerosis, editorial, Ann. Int. Med. **33**:250, 1950.

production of atherosclerosis in cholesterol-fed rabbits, chickens and hypothyroid dogs. Evidence is accumulating to suggest that hypercholesteremia is a common, although far from invariable, accompaniment of coronary atherosclerosis.[107] An explanation for some of the lack of association between cholesteremia and atherosclerosis arises from the experimental demonstrations that atherosclerosis is a function of a more or less disproportionate increase in cholesterol over serum phospholipid content. Thus, in biliary obstruction increases in cholesterol and phospholipid are concurrent, while in conditions associated with atherosclerosis the phospholipids do not keep pace.[108] Thus, also, the absolute and relative serum content of phospholipid is greater in children than in adults,[109] and an increase in serum lipid with age is more evident in pyknic than in leptosomatic body types.

But the age association of cholesteremia is still unsettled. Keys and his co-workers[110] found low values in adolescence, higher levels in the fifties and a decrease in old age. Sperry and Webb[111] surveyed their original group of normal men and women after a lapse of 13 to 15 years and found no change in more than half the group. The remainder—and what number of these are victims of latent atherosclerosis is anyone's guess—showed increases of 10 to 30 per cent in all men and all but one of the women.

The relation of diet and serum cholesterol is only now becoming clarified. In essential familial hypercholesteremia, Wilkinson and collaborators[112] found that the carbohydrate, fat, protein, caloric and cholesterol compositions of the diets had no relation to serum cholesterol. However, none of these diets was entirely fat and cholesterol free. The fat and cholesterol-free rice diet decreases serum cholesterol in patients with hypertension,[113] and fat-free diets which supply 2,000 to 4,000 calories cause prompt decreases in serum cholesterol (mean, 85 mg. per 100 cc.) in patients with gastrointestinal disease.[114] In normal subjects[115] diets in which the cholesterol content varies from 250 to 800 mg. daily have no effect on serum cholesterol, but the rice diet causes a prompt fall in serum level. Keys's data lead him to the view that "the general picture . . . is that the blood cholesterol level is independent of the intake over a wide range, but that at zero intake it falls at

107. Morrison, L. M., and Johnson, K. D.: Cholesterol Content of Coronary Arteries and Blood in Acute Coronary Artery Thrombosis, Am. Heart J. **39**:160, 1950.

108. Ahrens, E. H.: The Lipid Disturbance in Biliary Obstruction and Its Relationship to the Genesis of Arteriosclerosis, Bull. New York Acad. Med. **26**:151, 1950. Gertler, M. M.; Garn, S. M., and Lerman, S.: The Interrelationships of Serum Cholesterol, Cholesterol Esters, and Phospholipids in Coronary Artery Disease, Circulation **2**:205, 1950.

109. Kornerup, V.: Concentrations of Cholesterol, Total Fat and Phospholipid in Serum of Normal Man, Arch. Int. Med. **85**:398 (March) 1950.

110. Keys, A.; Mickelsen, O.; Hayes, R., and Miller, E.: Age and Serum Cholesterol Concentration in Normal Man, Federation Proc. **9**:69, 1950.

111. Sperry, W. M., and Webb, M.: Effect of Advancing Age on the Cholesterol Concentration of Blood Serum, Federation Proc. **9**:239, 1950.

112. Wilkinson, C. F., Jr.; Blecha, E., and Reimer, A.: Is There a Relationship Between Diet and Blood Cholesterol? Arch. Int. Med. **85**:389 (March) 1950.

113. Kempner, W.: Treatment of Hypertensive Vascular Disease with Rice Diet, Am. J. Med. **4**:545, 1948.

114. Mellinkoff, S. M.; Machella, T. E., and Reinhold, J. G.: The Effect of a Synthetic Fat-Free Dietary Regimen on Serum Cholesterol, J. Clin. Investigation **29**:834, 1950.

115. Keys, A.; Mickelsen, O.; Miller, E., and Chapman, C.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood, Science **112**:79, 1950.

a rate related to the previous level of cholesterol in the blood." Further observations suggest that, to be effective, a diet must be both fat and cholesterol free and not merely either fat or cholesterol poor.

In chicks treatment with estrogen, such as diethylstilbestrol, causes hyperlipemia and atherosclerosis, apparently as a result of increased lipid synthesis.[116] In this condition, as in the experimental cholesterol atherosclerosis of rabbits, desiccated thyroid is an effective lipotropic agent.[117] But the status of most other lipotropes hangs in doubt, although choline, methionine, inositol and such are commercialized for this purpose. Thus, in cholesterol-fed rabbits use of choline seems somewhat to decrease the incidence of aortic atherosclerosis, but its effect may also be related to the failure to gain weight during choline administration.[118]

Zinn and Griffith [119] have compared the proportions of large fat droplets (chylomicrons) to total fat droplets (lipomicrons) in normal subjects and in patients with arteriosclerosis and believe that there may be an increased content of the large particles in association with arteriosclerosis.

Moreton has developed in greater detail his view that the severity of hyperchylomicronemia and macrochylomicronemia may be a determinant of atherosclerosis and proposes a fat tolerance test to identify this tendency.[120] Another fat tolerance test is that of Stanley and Tannhauser [121] in which the estimate is made of the persistence of iodinated (I^{131}) fat in the blood stream after a standard dose of iodinated neutral fat. The latter test is essentially chemical, while the former is dependent on the physical state of circulating fat. Probably both aspects of fat transport have their significance. Thus, in rats—a species which does not display atherosclerosis on cholesterol feeding—test doses of radioiodinated fat cause only a briefly sustained rise in serum radiofat content; in rabbits, on the other hand, the curve rises much higher and is much more prolonged.[122]

But the most startling study of the year centers on the physical rather than the chemical state of the plasma lipoproteins. Interest in the fact that cholesterol and other lipids circulate in protein combination has grown with increasing interest in atherosclerosis, although technical difficulties retard any precise studies. However, Gofman and his co-workers [123] brought the ultracentrifuge to bear on the problem

116. Stamler, J.; Bolene, C.; Dudley, M., and Levinson, E.: Effect of Prolonged Exhibition of Diethylstilbestrol on Plasma and Tissue Lipids in the Chick, Endocrinology **46**:375, 1950.

117. Stamler, J.; Bolene, C.; Levinson, E., and Dudley, M.: The Lipotropic Action of Desiccated Thyroid in the Cholesterol-Fed Chick, Endocrinology **46**:382, 1950.

118. Moses, C., and Longabaugh, G. M.: Evaluation of Choline in the Prevention of Experimental Atherosclerosis, Arch. Path. **50**:179 (Aug.) 1950.

119. Zinn, W. J., and Griffith, G. C.: Number and Size of Fat Globules (Lypomicrons) in the Circulating Blood in Normal Individuals and in Patients with Coronary Disease, Am. J. Med. **8**:525, 1950.

120. Moreton, J. R.: Chylomicronemia, Fat Tolerance, and Atherosclerosis, J. Lab. & Clin. Med. **35**:373, 1950.

121. Stanley, M. M., and Tannhauser, S. J.: The Absorption and Disposition of Orally Administered I-131 Labeled Neutral Fat in Man, J. Lab. & Clin. Med. **34**:1634, 1949.

122. Masson, G. M. C.; Glasser, O.; Savard, K.; Corcoran, A. C., and Page, I. H.: Fat Tolerance Curves in Rat and Rabbit Using I-131, Am. Heart J. **38**:479, 1949.

123. Gofman, J. W.; Lindgren, F.; Elliott, H.; Mantz, W.; Hewitt, J.; Strisower, B., and Herring, V.: The Role of Lipids and of Lipoproteins in Atherosclerosis, Science **111**:166, 1950.

and have studied the rates of flotation of low density fatty proteins in solutions of a specific gravity of about 1.06. Their data suggest that lipoproteins with specific flotation rates (negative sedimentation rates) of 10 to 20 S_f units (*S* for Svedberg, *f* for flotation) occur in the serum in nearly every patient with proved myocardial infarction. They appear in many normal persons in a distribution by age and sex which corresponds well with that of subclinical arteriosclerosis. They develop during experimental atherosclerosis in rabbits. Thus, their distribution correlates so well with that of atherosclerosis as to suggest their intimate participation in the process. These workers discount the significance of such massive particles as the chylomicrons and find that normal plasma always contains certain fast-floating lipoproteins of 3 to 7 S_f units which have no untoward significance. A most important aspect of this study is the demonstration that diets which are poor in cholesterol lower the concentration of molecules of the S_f 10 to 20 class from abnormal to normal ranges. The correlations which they have demonstrated, although striking, are still not conclusive, and the whole problem is under extensive study.

In this connection, we have been greatly impressed by the extremely regular association of increased concentration of beta globulin—as measured by electrophoresis—with the presence of severe vascular disease. The association holds for patients or dogs with hypertension and for patients with diabetes and with a variety of other conditions.[124] The beta globulins measured include some of the lipoproteins, and it seems likely that a correlation can be shown between these globulins on the one hand and the particles of the S_f 10 to 20 class on the other. In a brief experience the elevations of beta globulin seem to have as much, or more, clinical and prognostic significance as the increases in the concentration of lipoprotein particles.

Hypertension of Endocrine Origin.—Current interest concentrates on the adrenal cortex and medulla. Clinically the hypertensive potentialities of the adrenal cortex are shown in the hypertension and nephrosclerosis which accompany Cushing's syndrome and by the hypertension sometimes observed as an untoward response to treatment with cortisone or ACTH.

Heinbecker [125] has added to his concept of the genesis of Cushing's syndrome. He views it as a state of pituitary imbalance with increased eosinophil and decreased basophil activity. Three distinct causes elicit this change. These are tumors of the adrenal cortex, atrophy of paired paraventricular hypothalamic nuclei and a progesterone-secreting tumor of the adrenal cortex. The nature of the pituitary imbalance has been masked in the past by the proliferation of hyalinized, functionally depressed basophil cells which are secondary to thyroidal and gonadal atrophy. The increased activity of the pituitary eosinophils stimulates those organs to which these cells are trophic, notably the adrenal cortex, the renal tubules, the corpora lutea and the androgenic cells of the testis. Hypertension results from combined adrenal cortex and renal pressor hyperactivity. Findley [126] has reviewed this concept with special reference to the possibility that it can be applied to the pathogenesis of essential hypertension.

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124. Lewis, L., and Page, I. H.: Studies on Lipoprotein in Dog Serum, Federation Proc. **8**:896, 1949.

125. Heinbecker, P., and Pfeiffenberger, M.: Further Clinical and Experimental Studies on the Pathogenesis of Cushing's Syndrome, Am. J. Med. **9**:3, 1950.

126. Findley, T.: Role of the Neurohypophysis in the Pathogenesis of Hypertension and Some Allied Disorders Associated with Aging, Am. J. Med. **7**:70, 1949.

In this connection, Schroeder and his associates [127] have described an "endocrine" hypertension in women which is characterized by girdle obesity, striae and responsiveness to restriction of dietary sodium. The inference is that these are in fact a *forme fruste* of Cushing's syndrome and that the hypertension is similar to that of the rat treated with desoxycorticosterone and salt. We have not, as yet, been able to characterize such cases.

As concerns essential hypertension, we agree with Perera,[128] who considers it doubtful that the solution to the problem of hypertensive vascular disease lies within the adrenal cortex. The best established adrenal cortex function in hypertension is one of maintenance of elevated arterial pressure as a function of general bodily homeostasis and not as a pathogenetic factor.[129] Evidence for adrenal participation in essential hypertension is still indirect. Many patients with hypertension tend to retain administered sodium somewhat unduly,[130] and the suggestion has been made that those normotensive persons who show this phenomenon may be in fact in a state of prehypertension.[131] Only a little more direct is the observation that some patients with essential hypertension excrete excess amounts of chloroform-extractable formaldehydogenic steroids in the urine.[132] However, the bulk of the urinary corticoid is excreted in bound form, presumably as a mixture of sulfates and glycuronides,[133] so that increased excretion, although doubtless often a reflection of increased formation, may sometimes only reflect a failure of steroid conjugation.

Actually, attempts to link the adrenal cortex with a mechanism of essential hypertension stem largely from the concept of essential hypertension as a "disease of adaptation" [134] which is dependent on an abnormal cortical hypersecretion of mineralocorticoids, such as desoxycorticosterone acetate or desoxocortisone.[38] The most that can be said is that direct evidence is wholly lacking, but that the concurrence of several concepts [135] which link adrenal and renal mechanisms seems at least to provide a field for more searching study; "where there's smoke . . ."

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127. Schroeder, H. A.; Davies, D. F., and Clark, H. E.: A Syndrome of Hypertension, Obesity, Menstrual Irregularities and Evidence of Adrenal Cortical Hyperfunction, J. Lab. & Clin. Med. **34**:1746, 1949.

128. Perera, G. A.: The Adrenal Cortex and Hypertension, Bull. New York Acad. Med. **26**:75, 1950.

129. Corcoran, A. C.: The Adrenal Cortex and Hypertension, in Symposium on the Adrenal Cortex, Dec. 1949, Washington, D. C., American Association for the Advancement of Science, to be published.

130. Perera, G. A., and Blood, D. W.: Disturbance in Salt and Water Metabolism in Hypertension, Am. J. Med. **1**:602, 1946.

131. Thomas, C. B.; Howard, E., and Issau, A.: Effect of Sodium Withdrawal on the Body Weight of Normal Young Men, J. Clin. Investigation **28**:814, 1949.

132. Corcoran, A. C.; Page, I. H., and Dustan, H. P.: Urinary Formaldehydogenic Corticoids: Normal Values and Observations in Hypertension, J. Lab. & Clin. Med. **36**:297, 1950.

133. Lieberman, S., and Dobriner, K.: Steroid Excretion in Health and Disease: I. Chemical Aspects, in Pincus, G.: Recent Progress in Hormone Research: Proceedings of Laurentian Hormone Conference, New York, Academic Press, Inc., 1948, vol. 3. Kinsella, R. A., Jr.; Doisy, R. J., and Glick, J. H., Jr.: Enzymatic Hydrolysis of Urinary Reducing Lipids, Federation Proc. **9**:190, 1950.

134. Selye, H.: Stress, Montreal, Canada, Acta, Inc., Medical Publishers, 1950.

135. Masson and others.[65] Heinbecker and Pfeiffenberger.[125] Selye.[134]

Quite recently, reports [136] have appeared in which bilateral total or subtotal adrenalectomy has resulted in remission in patients suffering from severe hypertension and whose conditions were otherwise desperate. The dangers are obvious, and the procedure must still be considered experimentally. From the theoretical point of view, the remission induced by adrenalectomy does nothing to prove that the adrenal gland is inherently concerned in the disease, since the decrease in arterial pressure can be better explained as a response to partial adrenal insufficiency.

The pheochrome tumors of the adrenal medulla, although uncommon, have considerable interest because they cause one of the few truly curable forms of hypertensive disease. Smithwick and his colleagues [137] direct attention to the importance of excessive perspiration, vasomotor instability, normal cold pressor responses, periodic increases in temperature, blood sugar and basal metabolic rate, glycosuria and postural tachycardia and hypotension as signs of diagnostic value. Cahill and Aranow [138] have reviewed the practical aspects of diagnosis and treatment, again directing attention to the fact that such tumors may cause persistent increases in arterial pressure, such as have been reported recently.[139]

The sympatheticomimetic activity of peripheral nerves and other extra-adrenal tissues has been shown to be due to their content of arterenol (nor-adrenaline). More recently, Bergström and his co-workers [140] have shown that arterenol is present together with epinephrine in extracts of beef adrenal gland, an observation extended to man by Savard in his laboratory. Bulbring and Burn [141] reported that arterenol is released with epinephrine from the adrenal glands in proportions varying from 20 to 80 per cent of the total pressor amine, and Holton [142] found twice as much arterenol as epinephrine in an extract of a pheochromocytoma. Goldenberg and Aranow [143] in 10 such tumors noted that arterenol constitutes 14 to 97 per cent of the total catechol. Their extensive study indicates that when the tumor is small and contains principally arterenol the hypertension is more commonly persistent and not paroxysmal. In seven of their 12 patients hypertension persisted for months or years after removal of the tumor, presumably as a sequel to nephrosclerosis and the vicious cycle mechanism of hypertensive disease. Epinephrine, in contrast to arterenol, causes more tachycardia, a greater increase in cardiac output, more

136. Green, D. M.; Nelson, J. N., and Dodds, G. A.: Effects of Adrenal Resection on Hypertension and Diabetes, Federation Proc. **8**:60, 1949. Guichard, A., and Boulliat, A.: Les lésions histologiques des capsules surrénales dans 32 cas d'hypertension artérielle permanente traitée par surrénalectomie, J. de méd. de Lyon **29**:203, 1948.

137. Smithwick, R. H.; Greer, W. E. R.; Robertson, C. W., and Wilkins, R. W.: Medical Progress: Pheochromocytoma, New England J. Med. **242**:252, 1950.

138. Cahill, G. F., and Aranow, H.: Pheochromocytoma: Diagnosis and Treatment, Ann. Int. Med. **31**:389, 1949.

139. Smith, H. P., Jr.; Logue, R. B., and Beard, D. E.: Sustained Hypertension Due to Pheochromocytoma, Circulation **1**:454, 1950.

140. Bergström, S.; von Euler, U. S., and Hamberg, U.: Isolation of Noradrenaline from the Suprarenal Medulla, Acta physiol. Scandinav. **20**:101, 1950.

141. Bulbring, E., and Burn, J. H.: Liberation of Noradrenaline from the Suprarenal Gland, Brit. J. Pharmacol. **4**:202, 1949.

142. Holton, P.: Noradrenaline in Adrenal Medullary Tumors, Nature, London **163**:217, 1949.

143. Goldenberg, M., and Aranow, H., Jr.: Pheochromocytoma and Essential Hypertension, J. Clin. Investigation **29**:816, 1950.

hyperglycemia and much more stimulation of pituitary release of ACTH. Arterenol is also somewhat less completely blocked by piperoxan hydrochloride (piperidylmethyl benzodioxane).[144]

Piperoxan hydrochloride is now widely used in the differential diagnosis of pheochromocytoma. In patients with essential hypertension intravenous doses of 10 mg. per square meter of body surface usually cause either no change or a slight increase in arterial pressure. The increase is sometimes considerable, so that Green and Peterson[145] believe that use of the drug precipitated hypertensive encephalopathy in a patient who had previously had similar attacks. Calkins and his collaborators[146] found only two of 112 patients surveyed for pheochromocytoma to show prompt and lasting decrease of pressure after injection of the drug. One of these was subsequently proved to have an arterenol-containing pheochromocytoma. The other was found to have a large cell neuroblastoma, the removal of which was followed by a decrease of pressure, although hypertension recurred with the recurrent tumor growth. Interestingly, piperoxan hydrochloride administration did not restore the pressure entirely to normal in the patient with the neural tumor. Taliaferro and his associates[147] have described a patient with hypertension of renal origin, who, on one occasion, showed a sharp fall in pressure after injection of piperoxan hydrochloride which could not subsequently be reproduced. It follows that a pressure drop induced with administration of piperoxan hydrochloride is not of itself diagnostic. Operative mortality varies up from 20 per cent. Death seems to be due to a shocklike state similar to that produced by massive doses of epinephrine,[148] precipitated by manipulation of the tumor. Grimson and others[149] and Bartels and Cattell[150] suggest, and report favorably on, the use of adrenolytic drugs during operation as a practical means of decreasing the operative risk.

Neurogenic Hypertension.—Hypertension produced in dogs by section of the carotid sinus and aortic depressor nerves continues to be largely of experimental interest. However, the late Prof. F. Volhard[151] drew attention to a possible participation of the sinodepressor mechanisms in essential hypertension. He reported that bilateral procaine block of the carotid sinuses causes a rise in arterial pressure which in hypertensive persons is severer and more prolonged than in persons with normal pressure. From this he suggested that hypertension is the result of a decreased sensitivity to increases of intra-arterial pressure on the part of baroceptors

144. Prunty, F. T. G.; Swan, H. J. C., and Wilson, G. M.: The Action of Benzodioxane in Man, with a Note on Negative Benzodioxane Tests, Lancet **1**:759, 1950.

145. Green, D. M., and Peterson, E. M.: Hypertensive Encephalopathy After Administration of Benzodioxan, J. A. M. A. **142**:408 (Feb. 11) 1950.

146. Calkins, E.; Dana, G. W.; Seed, J. C., and Howard, J. E.: Piperidylmethyl-Benzodioxane (933-F), Hypertension, and Pheochromocytoma, J. Clin. Endocrinol. **10**:1, 1950.

147. Taliaferro, I.; Adams, R. A., and Haag, H. B.: Benzodioxan Test, J. A. M. A. **140**: 1271 (Aug. 20) 1949.

148. Vigran, I. M., and Essex, H. E.: Studies on Physiologic Effects of Large Doses of Epinephrine, Am. J. Physiol. **162**:230, 1950.

149. Grimson, K. S.; Longino, F. H.; Kernodle, C. E., and O'Rear, H. B.: Treatment of a Patient with a Pheochromocytoma: Use of an Adrenolytic Drug Before and During Operation, J. A. M. A. **140**:1273 (Aug. 20) 1949.

150. Bartels, E. C., and Cattell, R. B.: Pheochromocytoma: Its Diagnosis and Treatment, Ann. Surg. **131**:903, 1950.

151. Volhard, F.: Ueber die Pathogenese des roten (essentiellen) arteriellen Hochdrucks und der malignen Sklerose, Schweiz. med. Wchnschr. **78**:1189, 1948.

other than those of the carotid sinuses. He related this decrease in sensitivity to impaired elasticity of the arterial walls, thus implying a primary morphological basis for hypertensive disease. The phenomenon deserves more searching analysis. Perhaps a cytochemical study would be revealing, such as that of Lansing and his co-workers [152] which demonstrated a shift in the composition of elastin with advancing age and an associated increase in calcium content.

We have previously advanced the concept of "neurogenic" hypertension as a state of established essential hypertension in which the predominant signs and symptoms are those of nervous hyperactivity, which suggests a nervous origin of the increased arterial pressure. Schroeder's classification included a similar group. A specific, more precisely defined "neurogenic" hypertension is that of the hypertensive diencephalic syndrome of Page. The mechanisms by which the central nervous system might cause any persistent increase in arterial pressure are not at all obvious. Various considerations, such as the fact that renal blood flow and cardiac output are normal in many patients with early hypertension, indicate quite clearly that the facile analogy of hypertension with the effects of epinephrine infusion or acute anxiety cannot be drawn, since epinephrine increases cardiac output and decreases renal blood flow. The suggestion has been made that infusion of arterenol closely mimics the hypertensive state.[153] However, the pressor responses so often obtained from injection of piperoxan hydrochloride tend to discount the assumption of excess arterenol secretion in hypertension. Of greater significance is the fact that extensive denervations in dogs result in sensitization to a variety of pressor agents, including renin and angiotonin.[154] This leads to the concept that central nervous system participation in hypertension is not the result of excessive stimulation but is rather a deprivation of a normal inhibitory function.

Hypertension of Unknown Origin.—We have elsewhere [155] defined essential hypertension as a "morbid state in which fluctuating systolic and diastolic arterial hypertension occurs in association with characteristic arteriolar vasoconstriction" and can add to this the statement that this disease, although its course is extremely variable, tends to progress in a more or less characteristic pattern toward failure of vascular adaptation and death from vascular damage.

Malignant hypertension (malignant phase of essential hypertension) is a state of rapidly progressive arterial hypertension, clinically associated with severe retinopathy (papilledema, hemorrhages and exudates), evidence of severe renal disease (proteinuria and hematuria) and weight loss.

The experimental and clinical considerations so far reviewed on the pathogenesis of essential hypertension leave us with no present hope that this problem will resolve into any unitary solution. Rather, essential hypertension seems to us a process comparable in some way to fever which has many and coordinate causes, although

152. Lansing, A. I.; Alex, M., and Rosenthal, T. B.: Calcium and Elastin in Arteriosclerosis, J. Gerontol. **5**:112, 1950.

153. Goldenberg, M.; Pines, K. L.; Baldwin, E. F.; Greene, D. A., and Roh, C. E.: The Hemodynamic Response of Man to Norepinephrine and Epinephrine and Its Relation to the Problem of Hypertension, Am. J. Med. **5**:792, 1948.

154. Page, I. H., and Taylor, R. D.: Augmentation of Vasoactive Substances by Tetraethylammonium, Circulation **1**:1233, 1950.

155. Page, I. H., and Corcoran, A. C.: Arterial Hypertension, Its Diagnosis and Treatment, ed. 2, Chicago, Year Book Publishers, Inc., 1949.

it presents itself under a single form. In this view, essential hypertension is a mosaic of altered vasomotor, endocrine and renal influences, any one of which may be predominant or the primary cause. Koepsell and his colleagues [156] report a clinical and pathogenic study of 39 cases of malignant hypertension, listing the principal clinical features of this condition—which they refer to as acute hypertensive cardiovascular disease—noting that exceptionally papilledema is absent or the urine normal or nearly so. They report one case in which there was a spontaneous remission lasting for 12 years.

Cortisone and ACTH may both, under suitable conditions, such as the provision of normal or excess dietary sodium, elicit definite increases in arterial pressure in susceptible normotensive patients. Paradoxically, Perera has proposed an antipressor action of cortisone in essential hypertension. The view is based in part on small decreases of "resting" arterial pressure observed during treatment with adrenal cortex extract,[157] on small downward trends observed in three patients treated with cortisone [158] and, in a large degree, on the response of one patient who received cortisone in a dose of 200 mg. daily for one month.[159] Even in this last patient the changes in arterial pressure do not seem to us significant. In four patients with severe essential hypertension, two of them treated with cortisone and two with ACTH, we were unable to demonstrate consistent or reproducible changes in pressure over periods of two to five weeks.[160]

An article in a popular magazine emphasizes the view that essential hypertension is often consistent with a normal life expectancy—which is, of course, true—but by implication at least suggests that the process is inherently benign and can be more or less disregarded. This point of view is in sharp contrast to our experience. A recent study of actual versus expected mortality rates in hypertension [161] clearly demonstrates the excess mortality incident to hypertensive disease and the greater mortality to men. Raaschou [162] has validated the clinical impression that hypertension is infrequent in hepatic disease by a survey of patients with subacute liver atrophy.

The cold pressor test remains under study with the unfortunate result that its initial promise wears thin. Thus, Bader and Mead [163] have shown that the rise of pressure in such tests is closely related to the perception of pain and does not

156. Koepsell, J. E.; Kuzma, J. F., and Murphy, F. D.: Hypertensive Cardiovascular Disease (Acute) (Malignant Hypertension), Arch. Int. Med. **85**:432 (March) 1950.

157. Pines, K. L.; Perera, G. A.; Vislocky, K., and Barrows, A. D.: Effects of Adrenal Cortical Extract in Hypertensive Patients, Proc. Soc. Exper. Biol. & Med. **68**:286, 1948.

158. Perera, G.; Pines, K. L.; Hamilton, H. B., and Vislocky, K.: Clinical and Metabolic Study of 11-Dehydro-17-Hydroxycorticosterone Acetate (Kendall's Compound E) in Hypertension, Addison's Disease, and Diabetes Mellitus, Am. J. Med. **7**:56, 1949.

159. Perera, G. A.; Fleming, T. C.; Pines, K. L., and Crymble, M.: Cortisone in Hypertensive Vascular Disease, J. Clin. Investigation **29**:739, 1950.

160. Dustan, H.; Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Cortisone and ACTH in Hypertension: The Establishment of Glycosuria, Proc. Am. Federation Clin. Research, to be published.

161. Frant, R., and Groen, J.: Prognosis of Vascular Hypertension: A 9 Year Follow-Up Study of 418 Cases, Arch. Int. Med. **85**:727 (May) 1950.

162. Raaschou, F.: Blood Pressure and Heart Weight in Chronic Hepatitis: Does Liver Play Part in Development of Essential Hypertension? Nord. med. **42**:1791, 1949.

163. Bader, M. E., and Mead, J. J.: Individual Differences in Vascular Responses and Their Relationship to Cold, J. Appl. Physiol. **2**:608, 1950.

correlate with digital vascular response to cold. Dihydroergocornine given intramuscularly partially inhibits the pressor rise,[164] but piperoxan hydrochloride does not.[165] These observations are in accord with the concept that the efferent arc of the pressor response is vasomotor and not humoral. In a seven year follow-up study of 166 officers, Armstrong and Rafferty[166] were unable to demonstrate that the cold pressor test had value as a means of predicting a hypertensive tendency. Somewhat similarly, Postelli and Palmer[167] found it of no help in the classification of the severity of hypertensive disease. In an unpublished survey made some years ago, we came to similar conclusions, having been impressed with our inability to reproduce the responses or to correlate them with prognosis. Indeed, responses seemed somewhat damped in many patients with malignant hypertension.

Cerebral Circulation.—The cerebral circulation has been vigorously explored, and its mechanisms have been admirably summarized.[94]

Some time ago we[168] found that hypertensive persons differ from normal persons in that their renal vessels, notably the afferent arterioles, fail to dilate as well during hypotension induced by spinal anesthesia. This residue of fixed resistance we attributed to afferent arteriolar sclerosis. Kety and his co-workers[169] now find that the cerebral vessels behave similarly and that rapid, severe decreases in arterial pressure result in decreasing blood flow and cerebral anoxia at pressure levels consistent with well-being in normotensive subjects.

Analogous to the effects of spinal sympathetic block are the responses of cerebral blood flow to tilting. In normal subjects flow is maintained in spite of a head-up position of 20 degrees by decreased cerebral vascular resistance. In hypertensive subjects after sympathectomy flow decreased in this position.[170]

The power of adjustment of the cerebral circulation is also shown by the effect of intramuscularly injected dihydroergocornine, which decreases arterial pressure in hypertension by an average of 38 mm. Hg mean pressure, while cerebral blood flow and oxygen consumption remain unchanged.[171]

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164. Freis, E. D.; Stanton, J. R.; Litter, J.; Culbertson, J. W.; Halperin, M. H.; Moister, F. C., and Wilkins, R. W.: The Hemodynamic Effects of Hypotensive Drugs in Man: II. Dihydroergocornine, J. Clin. Investigation **28**:1387, 1949.

165. Berris, B., and Agaard, G. N.: Effect of Piperidylmethyl-Benzodioxane on the Cold Pressor Response, Proc. Soc. Exper. Biol. & Med. **73**:287, 1950.

166. Armstrong, H. G., and Rafferty, J. A.: Cold Pressor Test: Follow-Up Study for 7 Years on 166 Officers, Am. Heart J. **39**:484, 1950.

167. Postelli, T., and Palmer, R. S.: Certain Pressor and Depressor Tests in Essential Hypertension: A Comparison and Comment, Am. Pract. **4**:9, 1949.

168. Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Circulatory Responses to Spinal and Caudal Anesthesia in Hypertension: Relation to the Effect of Sympathectomy: II. Effect on Renal Function, Am. Heart J. **36**:226, 1948.

169. Kety, S. S.; King, B. D.; Horvath, S. M.; Jeffers, W. A., and Hafkenschiel, J. H.: The Effects of Acute Reduction in Blood Pressure by Means of Differential Spinal Block on the Cerebral Circulation of Hypertensive Patients, J. Clin. Investigation **29**:402, 1950.

170. Crumpton, C. W.; Moyer, J. H.; Wendel, H.; Shenkin, H. A.; Jeffers, W. A., and Hafkenschiel, J. H.: Cerebral Blood Flow and Oxygen Metabolism Following Head-Up Tilt in Hypertensive Patients After Sympathectomy, Federation Proc. **9**:27, 1950.

171. Hafkenschiel, J.; Crumpton, C.; Moyer, J., and Jeffers, W.: Effects of Dihydroergocornine on the Cerebral Circulation in Patients with Essential Hypertension, J. Clin. Investigation **29**:408, 1950.

Aminophylline—which is usually considered to act in part by improving cerebral circulation—is, in fact, found to decrease cerebral blood flow and to increase vascular resistance and arteriovenous oxygen difference in normal subjects.[172] Confirmatory studies might well be carried out in patients with severe vascular disease and such aminophylline-responsive conditions as Cheyne-Stokes respiration. Somewhat similarly, stellate ganglion block has empirically been credited with profound therapeutic effects in cerebral vascular accidents due to arterial thrombosis or embolism.[173] However, in normal subjects or in patients with hypertensive and cerebral vascular disease stellate block does not alter cerebral blood flow or resistance.[174] The possibility remains that block may cause some redistribution of blood flow without changing either volume flow or oxygen consumption. Scheinberg [174b] also studied cerebral blood flow and metabolic functions in hypertensive patients with cerebral vascular disease, comparing those of normal with those of impaired mental status. Cerebral vascular disease without mental impairment is associated with decreased blood flow and increased vascular resistance, but oxygen and glucose utilizations were relatively normal. In contrast, patients with depressed mental status show greater depressions of blood flow, higher resistances and arteriovenous oxygen differences and depressions in the utilizations of both glucose and oxygen. The correspondence of cerebral metabolism and function is also shown in the toxemias of pregnancy, in which McCall [175] finds that blood flow and oxygen utilization are decreased in eclampsia, but not in preeclampsia.

Biomicroscopy of conjunctival vessels may prove a new and valuable tool in the study of hypertensive disease. Rather surprisingly, Lack and his associates [176] find changes more frequently in the capillaries than in the arterioles. The capillary changes consist in narrowing, elongation and looping with thickening of the walls and decreased distensibility. The severity of the capillary change correlates with the levels of diastolic arterial pressure. The changes are similar to those histologically found in cerebral capillaries in experimental hypertension.[1b]

TREATMENT

Methods of treatment of essential hypertension and hypertensive vascular disease have been increased in number and effectiveness within the recent memory of all of us. However, in the absence of definite pathogenetic concepts of this multiphasic syndrome, the selection of treatment depends on the status of the individual patient and a trial of the seemingly appropriate methods. Management is, in fact, deter-

172. Wechsler, R. L.; Kleiss, L. M., and Kety, S. S.: Effects of Intravenously Administered Aminophylline on Cerebral Circulation and Metabolism in Man, J. Clin. Investigation **29**:28, 1950.

173. Gilbert, N. C., and deTakats, G.: Emergency Treatment of Apoplexy, J. A. M. A. **136**:659 (March 6) 1948.

174. (*a*) Harmel, M. H.; Hafkenschiel, J. H.; Austin, G. M.; Crumpton, C. W., and Kety, S. S.: The Effect of Bilateral Stellate Ganglion Block on the Cerebral Circulation in Normotensive and Hypertensive Patients, J. Clin. Investigation **28**:415, 1949. (*b*) Scheinberg, P.: Cerebral Blood Flow in Vascular Disease of the Brain, Am. J. Med. **8**:139, 1950.

175. McCall, M. L.: Cerebral Blood Flow and Metabolism in Toxemias of Pregnancy, Surg., Gynec. & Obst. **89**:715, 1949.

176. Lack, A. L.; Adolph, W.; Ralston, W.; Leiby, G.; Winsor, T., and Griffith, G.: Biomicroscopy of Conjunctival Vessels in Hypertension, Am. Heart J. **38**:654, 1949.

mined by the clinician's estimate, by specific indications or by serial application of available procedures, which range from those that are simple and easy to those that are complex and drastic.

The first and most important aspect of treatment in all phases of the disease, especially early in its course, is the cultivation by every means available of serenity and the "good life." Clinical experience (without good statistical backing) uniformly subscribes to this rule; but the recent studies of Wolff and his group [177] provide the physiological basis for these simple recommendations in terms of the hypertensive person's complex hemodynamic responses to the situations of daily life. Briefly, patients with hypertension are shown to respond to minor stresses by abnormally and excessively prolonged increases of arterial pressure, cardiac output and peripheral resistance and by notable decreases in renal blood flow with considerable increase in arteriolar resistance. It is, therefore, of the essence that every patient with hypertension learn or be taught to avoid those stresses to which he cannot readily adapt himself, to adapt to the stresses of daily life which he cannot avoid and to take advantage as need arises of the solicitous concern of the physician and the quieting effect of crutches such as phenobarbital. He must recognize that he is in a measure crippled, and that like any cripple he must avoid the impossible, do what comes to hand and use the means of help which are available.

The control of obesity is a common need. In Frant and Groen's [161] nine year study of 418 patients with essential hypertension, they found that the coincidence of obesity and hypertension offered a better prognosis than high blood pressure in conjunction with normal weight. At first glance, this seems to contradict insurance data and clinical experience which show that obesity shortens life. However, when one considers that those patients with serious vascular disease not only die at an earlier age but lose weight because of their disease, it becomes clear that, as in diabetes, only those become fat whose disease is mild and they live longer in spite of obesity rather than because of it. Thus, in the individually prescribed dietary regimens, some of which may be more or less openly psychotherapeutic, it is wise to maintain body weight at average normal or subnormal levels by caloric restriction.

Drugs.—As symptoms become incapacitating or as evidences of failure of vascular adaptation arise, the simple measures should be supplemented by use of drugs known to depress blood pressure. Sodium thiocyanate is one of the oldest of these. It still has a definite place in the treatment of patients with severe headache.

In our experience 65 per cent of patients can thus obtain some degree of relief from this complaint. This effect can usually be achieved at serum thiocyanate concentrations as low as 3 to 6 mg. per 100 cc. This range is much lower than the 8 to 12 mg. per 100 cc. previously recommended.[178] Confirmation of our experience was furnished by Alstad,[179] who found that 62 per cent of 32 patients receiving thiocyanate were subjectively improved and had reduction of arterial blood pressure of greater than 15 mm. Hg systolic and 10 mm. diastolic. None felt as well or had

177. Wolff, H. G.: Life Stress and Cardiovascular Disorders, Circulation **1**:187, 1950.

178. Barker, M. H.: Blood Cyanates in Treatment of Hypertension, J. A. M. A. **106**:762 (March 7) 1936.

179. Alstad, K. S.: The Effects of Thiocyanate on Basal and Supplemental Blood Pressures, Brit. Heart J. **11**:249, 1949.

an equal fall of pressure with placebos. Fischmann and Fischman [180] found that 66 per cent of their patients had 10 to 25 per cent reduction of blood pressure. However, only one third of the patients had a rise in pressure when thiocyanate administration was discontinued. It is highly probable that the reduction of blood pressure incident to the administration of this drug results from its analgesic and sedative action and from the relief of symptoms. The decrease in arterial pressure is, therefore, probably secondary. It is none the less worth while.

Derivatives of Veratrum viride are more effective hypotensive agents than thiocyanate. However, their general use is limited by toxic vomiting. Meilman and Krayer [181] found that protoveratrine and veratridine given by vein reduced the blood pressure in patients with essential or renal hypertension. Krayer and Acheson [182] have earlier shown that this hypertensive response is primarily the result of a vasodilator reflex. The afferent pathway arises in the vessels of the heart and lungs and runs in the vagus nerves. The efferent vasodilator fibers are distributed through mixed nerves and are probably sympathetic. The hypotensive state is attended by bradycardia which can be blocked by atropine treatment without consistently influencing the fall of blood pressure. In these patients the T waves, previously flat or inverted in standard lead I of the electrocardiogram, often become upright. This change is common to patients given most hypotensive agents and under appropriate conditions occurs "spontaneously."

Wilkins, Stanton and Freis [183] reported favorable results in more than 50 per cent of hypertensive patients followed for five months during treatment with a partially purified Veratrum product called veriloid.® Wilkins later reported [184] that 80 per cent showed improvement as measured by average blood pressure while taking the drug. In most of these patients symptoms were concurrently relieved. However, the dosage was difficult to regulate because of nausea and vomiting, and as time went on effectiveness diminished. He stated that it was far from the ideal drug for the routine treatment of essential hypertension. Coe and his associates [185] treated 25 ambulatory patients with cruder preparations of Veratrum viride and controlled their study with administration of placebos. Sixty-four per cent improved with Veratrum, and 60.8 per cent had similar degrees of improvement with placebos. There were toxic symptoms in 64 per cent of those receiving Veratrum.

In our hands a small proportion of patients can take veriloid® in amounts sufficient to influence favorably the blood pressure. Those with essential hypertension who fall into this group usually show regression of the objective and subjective

180. Fischmann, E. J., and Fischman, A.: Thiocyanate in Hypertension: Blood Pressure Behavior After Withdrawal of the Drug, and Serial Electrocardiograms as Criteria of Response, Am. Heart J. **39**:477, 1950.

181. Meilman, E., and Krayer, O.: Clinical Studies on Veratrum Alkaloids: I. The Action of Protoveratrine and Veratridine in Hypertension, Circulation **1**:204, 1950.

182. Krayer, O., and Acheson, G. H.: The Pharmacology of the Veratrum Alkaloids, Physiol. Rev. **26**:383, 1946.

183. Wilkins, R. W.; Stanton, J. R., and Freis, E. D.: Essential Hypertension: Therapeutic Trial of Veriloid, A New Extract of Veratrum Viride, Proc. Soc. Exper. Biol. & Med. **72**:302, 1949.

184. Wilkins, R. W.: Veratrum Viride and Essential Hypertension, New England J. Med. **242**:535, 1949.

185. Coe, W. S.; Best, M. M., and Kinsman, J. M.: Veratrum Viride in the Treatment of Hypertensive Vascular Disease, J. A. M. A. **143**:5 (May 6) 1950.

signs of disease. Unfortunately, after a number of months tolerance to the drug diminishes, and treatment often must be discontinued. In those with the malignant syndrome our results have not been as striking. Only a few show reduction of blood pressure, and as a rule the progression to renal failure is not considerably retarded.

Dietary Treatment.—Brozek and his co-authors [186] reported that during the seige of Leningrad starvation caused reduction of blood pressure in some hypertensive patients and that hypertension was severely exacerbated by refeeding. On the other hand, no change of blood pressure was found among hypertensive patients on a starvation, low protein diet in Budapest.[187]

There is adequate and growing evidence [188] that the hypotensive effect of most dietary treatment of essential hypertension depends on sodium restriction. There are two limitations to this method [189]: 1. It is difficult for patients to follow a diet which restricts sodium sufficiently ($<$ 500 mg. per day). 2. The condition of only a limited number of patients responds to restriction of sodium. Kempner's rice diet [190] is a practical low sodium regimen which allows less than 200 mg. of sodium per day and, after an initial period of adjustment, can maintain a positive nitrogen balance. Peschel and Peschel [191] studied 12 patients, five of whom showed only a slightly negative nitrogen balance and seven a slightly positive one. We followed one patient on the rice diet who maintained approximate nitrogen equilibrium through a fracture of her hip, its surgical reduction and the period of recuperation.

In spite of the rice diet's virtues, only a few patients whose faith in it is not reenforced by evangelical fervor have the fortitude to adhere to it for a sufficient length of time. Thus, of 56 patients Loofbourow and his colleagues [192] observed only 16 who actually followed the diet for more than a few days or weeks. Of these 16 only six had significant reduction of blood pressure. Bang and others [188b] treated 26 patients with a low sodium diet and found some reduction of blood pressure in 16. Kert and his associates [189] studied 59 patients who were given a diet that allowed only 200 mg. of sodium per day. Of these only 36 followed the program; 25 per cent of the 36 had significant falls of blood pressure. However, all 59 showed

186. Brozek, J.; Chapman, C. B., and Keys, A.: Drastic Food Restriction: Effect on Cardiovascular Dynamics in Normotensive and Hypertensive Conditions, J. A. M. A. **137**: 1569 (Aug. 28) 1948.

187. Kohari-Kucharik, J.: The Effect of a War-Imposed Protein-Free Diet on the Blood Pressure Level in Essential Hypertension, Am. J. M. Sc. **219**:27, 1950.

188. (*a*) Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Controlled Observations on the Effect of Low Sodium Dietotherapy in Essential Hypertension, Circulation **3**:1, 1951. (*b*) Bang, H. O.; Bechgaard, P., and Nielson, A. L.: Low Salt Diet in Treatment of Hypertension and Hypertensive Heart Disease, Brit. M. J. **2**:1203, 1949.

189. Kert, M. J.; Rosenburg, M. J.; Coodley, E. L.; Murdock, L. J.; Hoffman, S. H.; Brotman, E. J., and Johnston, W. L.: Treatment of Hypertension: Experiences with the Use of a Low Sodium Diet Other Than the Rice Diet, J. A. M. A. **143**:721 (June 24) 1950.

190. Kempner, W.: Treatment of Heart and Kidney Disease and of Hypertensive and Arteriosclerotic Vascular Disease with the Rice Diet, Ann. Int. Med. **31**:821, 1949.

191. Peschel, E., and Peschel, R. L.: Nitrogen Balance on Rice Diet, J. Clin. Investigation **29**:455, 1950.

192. Loofbourow, D. G.; Galbraith, A. L., and Palmer, R. S.: Effects of Rice Diet on Level of Blood Pressure in Essential Hypertension, New England J. Med. **240**:910, 1949.

subjective improvement, with 87 per cent professing relief of headache. The authors pointed out that unless weekly measurement of urinary sodium was made there was no way of knowing that treatment was adequate.

We [188a] presented evidence that no dietary substances other than sodium had an effect on blood pressure. Strict adherence to the rice diet or measurements of output of urinary sodium are the only methods that insure adequate restriction of sodium. Our unpublished data, along with that of Berger and his co-authors,[193] indicate that cationic adsorbing resins, taken orally, can cause adequate sodium deprivation if the resin administration is combined with a diet which allows only 1 to 3 Gm. of sodium per day.

We also found that unless obvious subjective improvement and reduction of blood pressure occurred within four weeks it was useless to continue further. Cole [194] has pointed out that sodium in the water supply of many cities (often greater than 10 mg. per 100 cc.) can nullify effects of sodium restriction. The sodium content of water is increased by the use of water softeners.

In patients with advanced tubular disease, hyponatremia with oliguria and azotemia can supervene and must be constantly watched for. This syndrome and its management have been adequately described by Schroeder.[195]

In this connection we observed a particularly interesting patient with severe malignant hypertension. He exhibited advanced renal failure and a Tm_{PAH} (tubular maximal capacity for paraaminohippuric acid) of 12 mg. per 1.73 square meters per minute. After he followed the rice diet for four weeks, his blood pressure approached normal levels and other objective signs of disease receded. However, during the heat of the summer azotemia became pronounced in spite of a normal blood pressure, and oliguria appeared. The serum sodium level was found to be 115 milliequivalents per liter. The rice diet was continued, but only by the addition of 2 Gm. of sodium chloride per day to his diet could the hyponatremic state be controlled. Thus, some patients can achieve all the benefits of sodium restriction on a diet which is not sodium poor. But the balance is delicate, and in our patient provision of 2 Gm. of extra sodium chloride was followed by irreparable relapse of his condition.

Surgical Treatment.—Unilateral Nephrectomy: The therapeutic hopes which followed Goldblatt's production of experimental hypertension by clamping the renal artery to one kidney have faded because of the infrequency with which hypertension is relieved by removal of a diseased kidney. Occasional cases of unilateral renal disease do occur and should be sought for with at least as much diligence as the now more fashionable pheochromocytoma. Maitland [196] reported the cure of the malignant phase of hypertension in a woman 20 years old following removal of a diseased kidney. Gasul and his associates [197] removed a nonfunctioning pyelone-

193. Berger, E. Y.; Irwin, L.; Rosenberg, B., and Jackenthal, R.: The Effect of a Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States, J. Clin. Investigation **28**:770, 1949.

194. Cole, S. L.: Tap Water Sodium in the Low Salt Diet, J. A. M. A. **140**:19 (May 7) 1949.

195. Schroeder, H. A.: Renal Failure Associated with Low Extracellular Sodium Chloride: The Low Salt Syndrome, J. A. M. A. **141**:117 (Sept. 10) 1949.

196. Maitland, A. I. L.: Severe Hypertension with Recovery After Nephrectomy, Brit. M. J. **1**:46, 1949.

197. Gasul, B. M.; Glasser, J. M., and Grossman, A.: Extreme Hypertension in a Child Cured by Nephrectomy, J. A. M. A. **139**:305 (Jan. 29) 1949.

phritic kidney from a 9 year old child with malignant hypertension and found her status normal after two years. From the literature they were able to find only 31 other cases (22 of adults and nine of children) cured by nephrectomy. Doubtless, others have not been reported. We have observed two. It is a rare occurrence. Nonetheless, clinical and laboratory experience supports certain indications for nephrectomy in persons with high blood pressure. Generally, they should be the same as those for persons without hypertension. However, if it can be shown that the disease is of recent onset or that evidences of loss of vascular adaptation are slight or acute, one is justified in considering removal of the diseased kidney if its fellow is normal. This is all the more true if the patient is young and the family history is free of hypertensive disease.

Sympathectomy: That sympathectomy has a place in the treatment of essential hypertension is no longer questioned. However, application of this technic is limited by two real shortcomings: 1. Operation does not effect a "cure" in more than 15 per cent of patients. 2. There is no way of selecting these patients preoperatively. Hence many are operated on to no avail. For these reasons our indications for sympathectomy are (1) incapacitating symptoms that are not relieved by medical means, (2) evidences of advancing arteriolar disease that do not respond to medical measures and (3) early malignant hypertension.

The effectiveness of sympathectomy is probably best illustrated by the work of Hammarstrom and Bechgaard,[198] who followed 251 patients after sympathectomy and compared their longevity with that of 435 medically treated patients. Those operated on consistently lived years longer than those without operation. Keith and others[199] compared 96 patients treated medically with 56 who underwent operation. After three years those operated on had fewer symptoms, but the diastolic blood pressures of the two groups were about the same as at the initial study and the mortality rates were about equal.

Evans and Bartels[200] compared the results of two types of operations. In one the splanchnic chain and the eighth or the ninth to the twelfth thoracic ganglions and the second or third lumbar ganglion were removed; the other procedure extended upward to include the fourth thoracic ganglion. In follow-up studies of six months to three years they found the more extensive operation gave almost twice as many good results regardless of the type of hypertension involved. They observed, as have others, that much of the improvement was cardiac. The retinal signs in 78 of 117 patients improved. Operative mortality was 0.5 per cent, and over-all mortality at six to 33 months was 7 per cent.

In view of the good effects sympathectomy has been shown to have on the signs of hypertensive heart disease, Chavez and Mendez[201] applied this treatment to 11 patients with grade IV hypertensive heart disease that did not respond to the usual

198. Hammarstrom, M. D., and Bechgaard, P.: Prognosis in Arterial Hypertension: Comparison Between 251 Patients After Sympathectomy and a Selected Series of 435 Non-Operated Patients, Am. J. Med. **8**:53, 1950.

199. Keith, M. A.; Woolf, B., and Gilchrist, A. R.: The Results of Medical and Surgical Treatment of Essential Hypertension, Brit. Heart J. **11**:287, 1949.

200. Evans, J. A., and Bartels, C. C.: Results of High Dorsolumbar Sympathectomy for Hypertension, Ann. Int. Med. **30**:307, 1949.

201. Chavez, I., and Mendez, L.: Treatment of Hypertensive Heart Disease and Heart Failure of Hypertension, Am. Heart J. **37**:523, 1949.

measures. Three of these patients died within 10 months; eight improved, some enough to return to work. Although such an approach requires courage on the part of physician and patient alike, it is a defensible approach to treatment in admittedly irremediable congestive heart failure. In advising this, one assumes that rigid sodium restriction has been adequate and demonstrably ineffective. We advised bilateral thoracolumbar sympathectomy in one such case. The patient withstood both operations without incident. Within two weeks after operation he was free of edema for the first time in many months. However, within four months after surgical intervention congestive failure recurred, resisted conventional treatment and resulted in death.

Cerebrovascular disease of essential hypertension has not been so favorably influenced by sympathectomy as have the cardiac and retinal manifestations. As a matter of fact, cerebral changes of any considerable severity are contraindications to operation. Peet and Isberg [202] reported on their follow-up study of 125 patients who underwent bilateral splanchnicectomy after having shown signs of cerebral damage. After 10 years they could find no evidence that the course of the disease had been benefited. The mortality rate for this period was 40.5 per cent, but operative mortality is often severe in this group.

In view of the inevitable mortality rate, cost, etc., of even the simplest type of sympathectomy, it is surprising that paravertebral block by injection has not been more widely applied in the treatment of hypertension. Haxton,[203] of England, has suggested use of 10 per cent aqueous phenol. He has employed it in the treatment of 220 patients with peripheral vascular disease. Ninety per cent of these had warm, dry feet afterward. As he states, it is a procedure that can be easily and rapidly repeated.

MANAGEMENT OF COMPLICATIONS OF ESSENTIAL HYPERTENSION

Cerebral Thrombosis.—The management of cerebral thrombosis continues to be a relatively unsatisfactory effort. Harmel and his co-workers [174] have demonstrated that bilateral stellate block has no effect on cerebral blood flow or vascular resistance. The experience of others that patients with cerebral thrombosis are benefited by injection of procaine into the stellate ganglions cannot be ignored. It is possible that the nitrous oxide method of measuring total cerebral blood flow cannot detect minor changes which may occur in the zone of vasospasm near a small thrombus. Amyes and Perry [204] reported their experience in 44 patients with acute cerebral thrombosis or embolism treated with multiple stellate ganglion blocks. They noted improvement in 28 patients and in nine of 10 when treatment was started within the first six hours. In five of seven patients they reported marked improvement in the electroencephalogram after the first stellate block.

With the cooperation of Dr. W. James Gardner and members of his neurosurgical staff, our experience with blockade of the stellate and superior cervical ganglions has been extensive. The results have not been impressive. It is difficult

202. Peet, M. M., and Isberg, E. M.: Treatment of Hypertensive Cerebrovascular Disease by Splanchnicectomy, New England J. Med. **240**:319, 1949.

203. Haxton, H. A.: Chemical Sympathectomy, Brit. M. J. **1**:1026, 1949.

204. Amyes, E. W., and Perry, S. M.: Stellate Ganglion Block in the Treatment of Acute Cerebral Thrombosis and Embolism, J. A. M. A. **142**:15 (Jan. 7) 1950.

to control such a study with any degree of accuracy. By means of long term studies with control injections of isotonic sodium chloride solution it may be possible to evaluate this treatment to better effect in years to come.

Cerebral Hemorrhage.—Until the bold and sound attack of Wechsler and Gross [205] on the intracerebral hemorrhage, the usual approach to this complication was nihilistic. These workers described five patients in whom they were able to localize hematoma arteriographically. When the clot was evacuated surgically and the bleeding controlled, considerable neurological recovery followed and in two cases this was complete. The number of patients who will benefit from such treatment is small. However, the possibility of surgical relief should be considered in every case.

Although the past year has not included reports of rehabilitation by means of physical therapy, the aggressive program of Rusk [206] for reeducation of patients crippled by cerebrovascular disease should be mentioned. As soon as signs of bleeding are gone and consciousness permits, these patients should be out of bed and embarked on training to make them self sufficient in the routine of life. Surgeons generally have come to recognize the importance of early ambulation and rehabilitation. The same should be learned by internists called on to treat these disabling conditions.

CONGESTIVE HEART FAILURE

Studies of recent years have shed light on the mechanisms of heart failure and have provided rationales for what have become standard methods of treatment. Thus, the sequence of events which leads to tachycardia, dyspnea, paroxysmal nocturnal dyspnea and nocturia in congestive failure is now relatively clear. Huckabee and his co-workers [207] have pointed out that heart failure is always the result of reduction of cardiac output relative to inflow load. As failure supervenes in hypertensive heart disease, the left ventricle empties incompletely. This causes an increase in cardiac and pulmonary fractions of the blood volume above the normal of some 20 per cent, such as has been demonstrated in failure of the left side of the heart by Ebert and his collaborators.[208] The greater part of the increase is in the cardiac diastolic blood volume. Hence it is presumably localized to the left ventricle. Reduction of venous load by the upright position or by venous trapping by limb cuffs often dramatically relieves an attack of acute left ventricular failure because the disproportion between load and output is decreased.

McCann's [209] concepts are helpful as they concern the "cardiac asthma" associated with acute left ventricular failure. He thinks that the lungs serve as check valves between the ventricles. Thus, in early congestive failure due to hypertensive heart disease, it is likely that pulmonary vasoconstriction and bronchoconstriction

205. Wechsler, I. S., and Gross, S. W.: Arteriography in Cerebral Vascular Accidents, J. A. M. A. **139**:502 (Feb. 19) 1949.

206. Rusk, H. A.: Rehabilitation, Report of Council on Physical Medicine and Rehabilitation, J. A. M. A. **140**:286 (May 21) 1949.

207. Huckabee, W.; Casten, G., and Harrison, T. R.: Experimental Hypervolemic Heart Failure: Its Bearing on Certain General Principles of Heart Failure, Circulation **1**:343, 1950.

208. Ebert, R. V.; Borden, C. W.; Wells, H. S., and Wilson, R. H.: Studies of the Pulmonary Circulation, J. Clin. Investigation **28**:1134, 1949.

209. McCann, W. S.: Some Neglected Aspects of Cardiology: Circulatory Function of the Respiration, Am. J. Med. **8**:62, 1950.

occur in the attempt to relieve the poorly emptying left ventricle. If this is so, the beneficial effects of aminophylline given intravenously or rectally for the relief of "cardiac asthma" can be more readily explained from its established pulmonary action than from assumed effects on the heart muscle as such.

Ahmed and his colleagues [210] have done much to clarify the action of digitalis glycosides and their role in the treatment of the failing left ventricle. They compared the effects of ouabain and digoxin in normal men and in patients with congestive failure. Ouabain had no effect on normal hearts, but in left ventricular failure it increased cardiac output with a secondary fall of venous pressure. Digoxin had essentially similar effects but differed in that the venous pressure fell more in proportion to the change in cardiac output. They concluded that ouabain directly stimulated the myocardium and modified their previous view in which the action of digoxin was taken to be primarily venous. Ferrer [211] and Harvey and their associates [212] demonstrated that digoxin given to patients with left ventricular failure increased stroke volume and cardiac output, while pulmonary arterial pressure fell. They felt the drug had its primary effect on the myocardium.

The mechanisms of retention of sodium and water in congestive failure are probably multiple. It is now generally agreed that decreased glomerular filtration of sodium is one of them. Normally, sodium is believed to be reabsorbed from the tubular fluid in two phases. The "obligatory" phase in the proximal tubule accounts for approximately 85 per cent of filtered sodium; the residual 15 per cent passes into the distal tubule where it is available for reabsorption according to need, i. e., facultatively. A decreased tubular sodium load due to experimental decreases in filtration rate seems to result in an increased proportion of "obligatory" reabsorption or at least in sodium retention.[213] In congestive failure the decrease in load is due to a decreased glomerular filtration. Thus, the concept of glomerulotubular imbalance as a mechanism of sodium retention is validated experimentally. But this does not exclude participation of other mechanisms in the sodium retention of heart failure, such as, for example, increased facultative reabsorption in the distal tubules.

The therapeutic and prophylactic effects of restriction of dietary sodium to less than 1 Gm. per day are manifest in decreased edema and lessened recurrence of heart failure. The mechanism of action of the mercurial diuretics has been clarified by the evidence presented by Duggan and Pitts,[214] who attribute mercurial natriuresis

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210. Ahmed, S.; Bayliss, R.; Briscoe, W., and McMichael, J.: The Action of Ouabain (G-Strophanthin) on the Circulation in Man and a Comparison with Digoxin, Clin. Sc. **9**:1, 1950.

211. Ferrer, M.; Harvey, M.; Cathcart, R.; Webster, C.; Richards, D., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Digoxin in Cor Pulmonale, Circulation **1**:161, 1950.

212. Harvey, R.; Ferrer, M.; Cathcart, R.; Richards, D., Jr., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Digoxin in Left Ventricular Failure, Am. J. Med. **7**:439, 1949.

213. Selkurt, E.; Hall, P., and Spencer, M.: Influence of Graded Arterial Pressure Decrement on Renal Clearance of Creatinine, P-Aminohippurate and Sodium, Am. J. Physiol. **159**: 369, 1949.

214. Duggan, J., and Pitts, R.: Studies on Diuretics: I. The Site of Action of Mercurial Diuretics, J. Clin. Investigation **29**:365, 1950. Pitts, R., and Duggan, J.: Studies on Diuretics: II. The Relationship Between Glomerular Filtration Rate, Proximal Tubular Absorption of Sodium and Diuretic Efficacy of Mercurials, ibid. **29**:372, 1950.

to a depression of distal tubular reabsorption of sodium. This contrasts with previous functional and histopathological indications which lead to the concept that mercurial diuretics acted on the proximal tubules. Their data can explain failure of mercurial diuresis in conditions in which an increase in the proximal tubular sodium reabsorption fraction leaves little for mercury to act on in distant tubules. This view, however, is not generally accepted.

The greater efficacy of parenterally administered mercurials is generally known. Threefoot and his co-authors [215] presented studies with a radiomercury-tagged mercurial preparation which explained the reason for this. There was rapid urinary excretion of the injected material with inhibition of sodium reabsorption but very slow excretion from that given orally, probably because of slow and unpredictable absorption.

There are now extensive studies [216] which show the efficacy of the new subcutaneously injectable product, mercaptomerin (thiomerin®). However, the risk of hyponatremia with resulting extrarenal azotemia seems to contraindicate long-continued administration without medical supervision.

MALIGNANT PHASE

As noted above, the malignant phase of essential hypertension is characterized by the appearance of papilledema with hemorrhagic retinopathy, proteinuria and hematuria, as well as unexplained recent weight loss. Its management depends on the phase of the disease presented. If detected early in young persons, sympathectomy should be advised. However, if the process is well established and renal function is not depressed below 40 per cent of average normal as measured by the ability to excrete paraaminohippurate, treatment with bacterial pyrogens [217] arrests the signs of necrotizing arteriolitis in many patients.

If the process has progressed until renal function is below 40 per cent of normal, the best recourse is rigid sodium restriction. As Kempner [190] and we [189] have demonstrated, this regimen will salvage an occasional patient from almost certain death.

Uremia.—Save for 1 or 2 per cent of persons with essential hypertension who die of renal failure, most hypertensive persons who have uremia are in the malignant phase. When nitrogen retention is present, the prognosis is extremely grave. Nonetheless, all patients should have a trial with dietotherapy. Objectives of diet

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215. Threefoot, S.; Ray, C.; Burch, G.; Gronvich, J.; Milnar, J.; Overman, W., and Gordon, W.: Concentration, Time and Course in the Plasma of Man of Radiomercury Introduced as a Mercurial Diuretic, J. Clin. Investigation **28**:661, 1949.

216. Batterman, R. C.; Unterman, D., and DeGraff, A. C.: The Subcutaneous Administration of Mercaptomerin (Thiomerin®), J. A. M. A. **140**:1268 (Aug. 20) 1949. Stewart, H.; McCoy, H.; Shepard, E., and Luckey, E.: Experience with Thiomerin, a New Mercurial Diuretic, Circulation **1**:502, 1950. Grossman, J.; Weston, R.; Edelman, I., and Leiter, L.: Studies on Thiomerin, a Subcutaneous Administerable Mercurial Diuretic, Circulation **1**:508, 1950.

217. Taylor, R. D.; Corcoran, A. C., and Page, I. H.: Further Experience with Bacterial Pyrogens in the Treatment of Malignant Hypertension, Proc. Central Soc. Clin. Research **22**:83, 1949. Page, I. H., and Taylor, R. D.: Treatment of Malignant Hypertension with Pyrogens, Mod. Concepts Cardiovas. Dis. **18**:51, 1949.

are to reduce protein and sodium intake maximally. The most certain and simple way to accomplish this in such emergencies is with Kempner's rice diet.[190] Should the response be favorable, a more liberal diet can be given at a later date.

Adrenalectomy.—The association of hypoadrenalism with hypotension, of Cushing's syndrome with hypertension, the experimental hormonal hypertensions and the probability that adrenal substitution therapy will become easy and inexpensive have led to reexploration of adrenalectomy in the treatment of this otherwise hopeless disease. Green, Nelson and Dodds[136] have reported reversal of the malignant syndrome and survival after bilateral adrenalectomy. The patient was maintained in apparent good health with the use of cortical extracts and desoxycorticosterone. These results and recent advances in adrenal physiology have stimulated active study in our laboratory and others of this experimental approach to the treatment of arterial hypertension. It is clear that with present technics it is to be considered as a clinical experiment for trial in otherwise hopeless cases.

News and Comment

ANNOUNCEMENTS

Supplementary Edition of Motion Picture Reviews Now Available.—The Committee on Medical Motion Pictures of the American Medical Association has completed the first supplement to the second revised edition of the booklet entitled "Reviews of Medical Motion Pictures." This supplement contains 86 reviews of medical and health films reviewed in *The Journal of the American Medical Association* from Dec. 31, 1949 to Jan. 1, 1951. Each film has been indexed according to subject matter. The purpose of these reviews is to provide a brief description and an evaluation of motion pictures which are available to the medical profession.

Copies of this supplement are available upon request to:

The Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10, Ill.

Book Reviews

Serology with Lipid Antigen, with Special Reference to Kahn and Universal Reactions. By Reuben L. Kahn, D.Sc. Price, $6. Pp. 327. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

This book approaches the question of serologic tests from an unusual and interesting point of view. Positive reactions between blood serum and lipid antigens are shown to occur in normal persons, and only under carefully regulated conditions do they become diagnostic of syphilis.

The first and last sections of the book are devoted to a discussion of the "universal serologic reaction." The procedure to which this term is applied was devised by Kahn and consists of a series of quantitative Kahn tests set up in 10 different concentrations of sodium chloride solution, from 0 to 2.1 per cent, and with serum dilutions ranging from 1 to 640. The results are read immediately and after four and 24 hours of ice box incubation.

In the lower and higher salt concentrations, some flocculation always occurs, particularly at the four and 24 hour readings. The standard quantitative Kahn test with 0.9 per cent saline solution is near the middle of the battery of tests, and its reaction is usually completely negative in normal persons. However, there is a considerable degree of variation, and some normal persons show precipitation zones that approach very close to the 0.9 per cent column, from either the low or the high salt concentrations, and a few actually reach it. These, of course, would give biologic false positive reactions in the standard Kahn test for syphilis.

There are some variations in the patterns of flocculation in the universal reaction that may help to differentiate between syphilis and yaws. In leprosy, flocculation occurs in all salt concentrations but the pattern is different from that seen in syphilis. In tuberculosis and malaria flocculation occurs in a manner that Kahn thinks is distinctive enough to be of value in the diagnosis or the estimation of activity. However, several of the examples presented resemble some of the normal reactions so closely that the usefulness of the universal reaction in these diseases is dubious.

The technique of the Kahn test and its application in the diagnosis of syphilis are discussed in detail. The importance of keeping any test used in clinical diagnosis insensitive enough to avoid false positive reactions, even at the expense of a considerable loss of sensitivity, is emphasized.

It is refreshing to read a book on serology written by a serologist who is so thoroughly aware of the nonspecificity of the lipid antigen tests and who appreciates the great injury that is done to a person in whom an erroneous diagnosis of syphilis is made because of a false positive reaction.

Microphthalmos and Anophthalmos With or Without Coincident Oligophrenia: A Clinical and Genetic-Statistical Study. By Torsten Sjögren and Tage Larsson. Translated by Erica Odelberg. *Acta psychiatrica et neurologica*, supplement 56. Price, 15 Swedish crowns. Pp. 103, with 8 figures and 20 tables. Ejnar Munksgaards Forlag, Nørregade 6, Copenhagen, Denmark, 1949.

In Sweden the registration of disease is particularly complete in the case of blind and deaf-mute children whose education must take place in special schools. In a survey of this material the authors found 51 probands of microphthalmos or anophthalmos with oligophrenia (MO) and 79 probands of microphthalmos or anophthalmos without oligophrenia during the period 1879 through 1946. If the combination of microphthalmos and oligophrenia were strictly random, about 0.68 $\pm$ 0.1 per cent (incidence of oligophrenia in the general Swedish population) of the 160 patients with microphthalmos would be expected to have oligophrenia also. The actual figure is about 60 times this, demonstrating that the combination must be regarded as a homogenous form of the disease or the two must be linked strongly. Among the cases

of microphthalmos or anophthalmos with oligophrenia there was also a high incidence of skeletal anomalies, i. e., flatfeet, clubfeet and kyphosis (64 per cent), and of epilepsy (about 30 per cent). In 40 of the 49 families of these probands studied there were no other cases; there were two cases in six families and three in one, all the affected children being of the same sex. A study of the family pedigrees in these cases indicated the most probable mode of inheritance to be partially sex linked with a reduced degree of penetrance. The possibility was not excluded that there are different modes, such as mutations with dominant appearance or totally sex-linked mode in certain cases. Analysis of isolated cases of microphthalmos is based on 65 cases in 59 families. Pedigree charts of families affected indicate a dominant mode of inheritance, and it is suggested this is the probable mode in most cases with a decreased penetrance.

Extrinsic Factors in Carcinogenesis. By Oluf Poulsen. No price given. Pp. 248. H. K. Lewis & Co., Ltd., 136 Gower St., London, England, 1949.

This publication presents the report of a fairly extensive study of the "tumor acceleration phenomenon" induced by known and suspected carcinogens. The author defines the acceleration phenomenon as "an increase of the incidence and/or a reduction of the age of appearance of the tumors."

Along with the report of the results obtained from his own investigations, the author presents a comprehensive review of the pertinent literature and a critical appraisal of the reports made by other investigators.

Suspected carcinogens from dietary sources were studied, but no significant evidence was obtained that would warrant the recommendation of a radical change in the diet or mode of living now followed by civilized nations. However, it does appear from this study that retardation in the incidence and growth of cancer might follow a restriction of certain luxuries and a moderate quantitative reduction of diet, particularly at the cost of fatty substances, in persons of the age groups above 40 years.

Die Wirkungseinheit des Lebens: Eine Einheits-, Spezial- und Ganzheitsbetrachtung der Lebensvorgänge unter normalen und krankhaften Bedingungen. By Ludwig Seitz, M.D., previously Professor of Gynecology, University of Frankfort-am-Main. Price, 33 German marks. Pp. 500, with 54 illustrations. Urban & Schwarzenberg, Thierschstrasse 11, München 2; Meinekestrasse 13, Berlin W. 15, Germany, 1950.

The first difficulty confronting the reviewer is an adequate translation of the title of this book! One would be "The Functional Unit of Life: Processes of Life in Normal and Pathological Conditions; Their Unity, Specificity and Totality." The author was led to his conception of a working unit by the energy quantum theory of Planck. So he takes the cell, together with its interaction with its physical and chemical environment as a physiocellular or functional or biologic working unit. The relationship of this biologic working unit (B) to its two determining factors, the cell or rather its minute morphologic structure (m) and the stimulating physical agent (including chemical), is expressed in an equation $B = a.r.m.$ In contrast to the quantum, which is a constant, all the members of the equation are variable.

It is hardly likely that such a conception will find much favor. The fine composition of the cell and its structure give rise to the smaller physiosubmicrocellular (physiomicellar) working units within the cell, which are differentiated in plasma nuclear, nucleochromosomal and chromosomalgenic action units. Chemical and biomorphologic structures are distinguished. For instance, genes are chemical structures (nucleoprotein), while chomosomes are biomorphologic structures. It may be mentioned that the reservation of nucleoproteins for the nucleus of the cell is no longer tenable. The production of specific substances, for example, myosin or casein, is dependent on the smallest submicroscopic cell structures and deviation of these from the normal is assumed to determine the formation of malignant tumors. To make the cell capable of performing its tasks, outside factors depending on circulation and nervous stimulation are necessary. The specific chemohormonal working units in their relation to metabolism, propagation and especially pregnancy form the subject of special chapters. The physioelectro-

cellular action units of the nervous system are the subject of another. In the chapter on the vegetative nervous system and vegetative reflexes a subdivision denies that a general increased tonus of either the sympathetic or the parasympathetic nervous system occurs.

The chemohormonal and neural control of the circulation of the blood and its distribution are summarized in a dictum of H. Rein, "The circulation must do what the metabolism demands." Special chapters deal with the control of body temperature, with water metabolism and its essential changes and disturbances in the cell and in the organism. This chapter ends with the remark that the water metabolism of the cell is far from being clarified. Carbohydrate metabolism and diabetes mellitus, fat metabolism, normal and abnormal, as well as its combined humoral, hormonal and neural control, are the subjects of other chapters. The main role in fat metabolism is given to the peripheral fat cells. Of the 65 chapters only a few have been mentioned to give an idea of the book, which, although it presents many interesting features, could be considerably shortened without harm to the main objective.

The author combats the overemphasis which has been accorded to the neurovascular or nervous system with reference to physiology and pathology. The cell remains the most important unit of the organism and demands a more searching investigation of its biomorphologic configuration and of the forces at work within its confines, with due regard to the physical and chemical factors of its environment which maintain the metabolism of the cell and organism.

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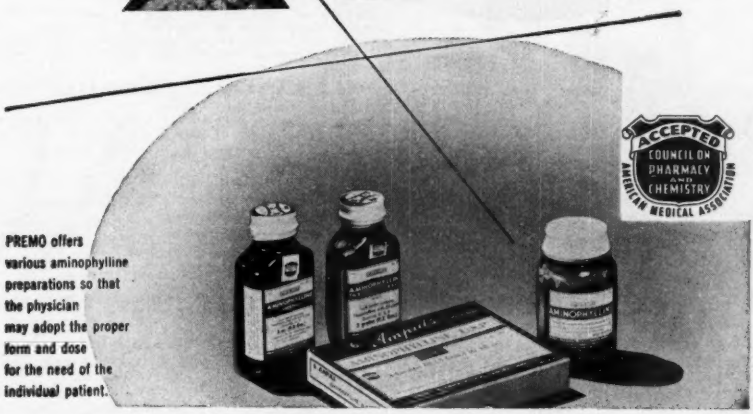

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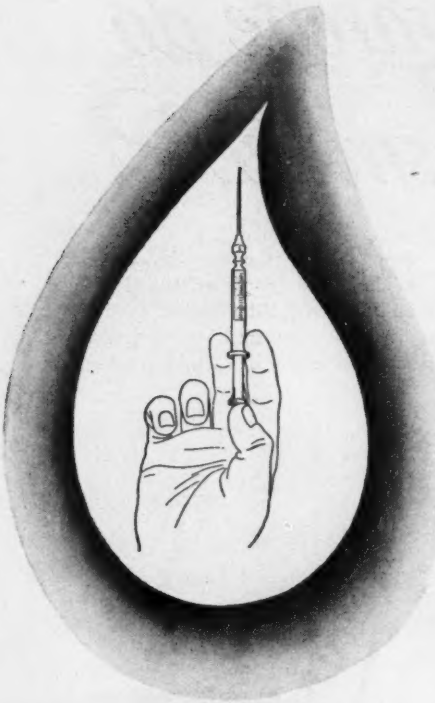

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BIBLIOGRAPHY

(1) Tompsett, R., and McDermott, W., Am. J. Med. *7*: 371-381, Sept. 1949. (2) Tompsett, R., Ann. Otol., Rhin. & Laryng. *57*: 181, March 1948. (3) Sweany, H. C., Dis. Chest *15*: 631-656, June 1949. (4) Lincoln, S., Science News Letter *55*: 307, May 14, 1949. (5) Semans, J. H., J. M. A. Georgia *38*: 477-480, Nov. 1949. (6) Domon, C. M., Kilbourne, P. C., and King, E. Q., Amer. Rev. Tuberc. *60*: 564, 575, Nov. 1949. (7) Nagley, M. M., Brit. M. J. *1*: 248, Jan. 28, 1950 (in correspondence). (8) Committee on Medical Research and Therapy, American Trudeau Society, Am. Rev. Tuberc. *61*: 436-440, March 1950. (9) Carr, D. T., Hinshaw, H. C., Pfuetze, K. H., and Brown, H. A., Dis. Chest *16*: 801-821, Dec. 1949. (10) Odell, J. M., Dis. Chest *16*: 818, Dec. 1949. (11) (Editorial) New England J. Med. *240*: 736, May 5, 1949. (12) Keefer, C. S., Ann. Int. Med. *33*: 582-589, Sept. 1950. (13) Marsh, D. F., W. Va. Med. J. *45*: 280-284, Oct. 1949. (14) Johnson, H. M., J. Invest. Dermat. *15*: 61-66, July 1950. (15) Hinshaw, H. C., Personal communication. (16) Lincoln, N. S., Horton, R., Stokes, A. M., Monroe, J., and Riggins, H. M., Am. Rev. Tuberc. *62*: 572-581, Dec. 1950. (17) Carr, D. T., Brown, H. A., Hogson, C. H., and Heilman, F. R., J. A. M. A. *143*: 1223-1225, Aug. 5, 1950. (18) Jacoby, A., Goldberg, W., Sobel, N., and Rosenthal, T., Am. J. Syph., Gonor. & Ven. Dis. *34*: 185-186, March 1950.

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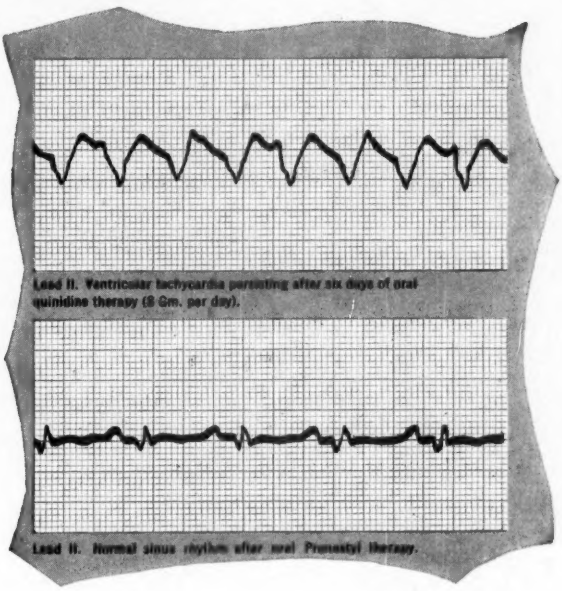

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